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ACUTE STAPHYLOCOCCUS OSTEOMYELITIS

THE USE OF STAPHYLOCOCCUS ANTITOXIN AS AID TO MANAGEMENT OF TOXEMIA AND STAPHYLOCOCCEMIA

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STAPHYLOCOCCI produce either a number of exotoxins or one exotoxin which has a variety of biological effects. A leucocidin was demonstrated by Van de Velde (31) in 1894; an hemolysin, by Kraus and Clairmont (19) in 1900 and by Neisser and Wechsberg (21) in 1901; a rapidly acting lethal toxin, by Kraus and Pribram (20) in 1906; and a dermal necrotizing toxin by Parker (27) in 1924. Subsequent studies by Nicolle and Cesari (23), Parker and Banzhof (28), Burnet (5), Gross (11), Panton and Valentine (24), Bigger, Boland, and O'Meara (1, 2), Burky (4), Combiesco, Istrati and Combiesco (6), Connor and McKie (7), Forssman (10), Nelis (22), Parish and Clark (26), Birch-Hirschfeld (3), Dolman (8), Jamieson and Powell (16), Weld and Gunther (32), Pike (29), Hartley and Smith (15) indicate that many strains of staphylococci produce all of these exotoxins and that the exotoxins from any one strain will stimulate the formation of antitoxin capable of neutralizing the toxins produced by any other strain of staphylococcus.

Encouraging results have been obtained with antitoxin treatment in a total of more than one hundred patients by Panton, Valentine, and Dix (25); Gross (12, 13, 14), Parish, and Clark (26), Dolman (9), and Keith (18). The largest and best controlled series of cases was reported by Dolman.

Our interest in this problem began in 1932 with the isolation of a hemolytic Staphylococcus aureus from the throat of a patient dying with malignant neutropenia (Tolly strain). This organism produced leucocidins, hemolysins, dermal necrotizing toxins, and a lethal toxin which would kill rabbits in 3 to 10 minutes. Injections of graded doses of this toxin into rabbits over a period of 6 to 10 days resulted in a hyperplasia of the bone marrow (similar to that shown by the marrow of the patient), an increase in the non-segmented and a decrease in the segmented polymorphonuclear leucocytes of the circulating blood and a fluctuating neutropenia (17). Necropsies on the rabbits showed a cortical necrosis of the kidney (30).

After testing the potency of our toxin in over 150 rabbits under various conditions, we obtained a supply of staphylococcus antitoxin[2] prepared from the toxin produced by Burky's Ha strain of hemolytic Staphylococcus aureus. We found that this antitoxin protected completely 16 rabbits from the effects of multiple lethal doses of toxin from our original strain (Tolly) while 16 unprotected control animals died in from 3 to 15

[2]Product of Lederle Biological Laboratories.

[1]Aided by the Henry Strong Denison Medical Foundation and the Bowman Gray Medical Research Fund.

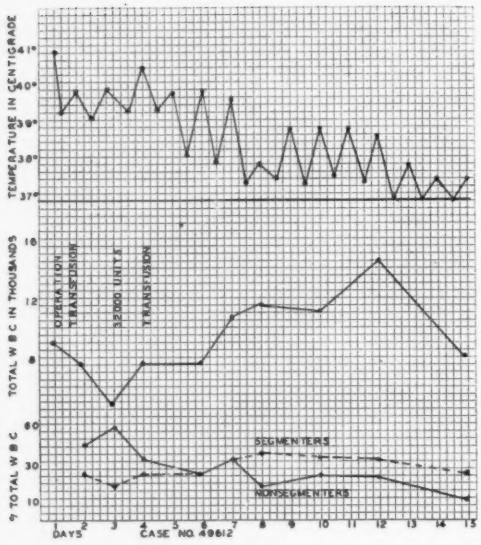

Fig. 1. Case 49612. Shows temperature chart and hemogram of a 2 year old child with acute osteomyelitis and staphylococcemia. This illustrates the recovery following a single dose of antitoxin.

minutes. It also protected rabbits from potent toxins made from three other strains isolated from patients with various types of staphylococcus infections.

We noted that the severity of the toxemia in the experimental rabbits could be estimated by the shift in the percentage of the segmented to non-segmented polymorphonuclear leucocytes rather than from the total white blood count. The same type of hemogram was found in certain patients with acute staphylococcus disease.

In 11 children with acute osteomyelitis and staphylococcemia, the administration of staphylococcus antitoxin was followed by marked improvement in the general condition of the patient attended by a decrease in the percentage of non-segmented with an increase in the segmented polymorphonuclear leucocytes. All 11 of these patients survived the acute stage of the disease although one child died 6 months later of cardiac failure due to pyopericarditis. Two children with acute osteomyelitis and staphylococcemia, who failed to show improvement in the hemogram after antitoxin treatment, became rapidly worse and died. All 13 of these children received the usual treatment for acute osteomyelitis consisting of prompt drainage and multiple blood transfusions in addition to the administration of antitoxin. Fifteen other children and one adult with acute osteomyelitis and staphylococcemia received the same treatment except for the antitoxin. The adult and 7 children died in the acute stage of the disease. This is a mortality of 50 per cent which Dolman says is the usual mortality for acute osteomyelitis with staphylococcemia.

Two patients with acute staphylococcus osteomyelitis with toxemia but without staphylococcemia were treated with antitoxin, and both recovered. Eight similar patients received the same treatment except for the antitoxin; 7 recovered and 1 died.

Case 49612. C. McC., a white male, 2 years and 6 months of age, was admitted to the hospital on March 1, 1935, with the complaint of fever and pain with increased heat and swelling over the lower end of the right tibia of 2 days' duration. The symptoms followed a mild trauma to the tibia 3 days before admission. The patient was acutely ill, somewhat disorientated, and presented an area of swelling, increased heat, and extreme tenderness over the internal malleolus of the right tibia. This area was immediately incised and drained by Dr. L. Ziv. Two transfusions of citrated blood were administered during the next 3 days, but the patient remained acutely ill with the temperature ranging between 39 and 41 degrees C. On the fourth day, the white blood count was 5,000 with 25 per cent segmented and 45 per cent non-segmented polymorphonuclear leucocytes (Fig. 1). He was given intramuscularly 40 cubic centimeters (32,000 P. international units) of staphylococcus antitoxin (Lederle). Another transfusion was given on the fifth day. Blood cultures taken on the fifth day showed per cubic centimeter of blood one colony of hemolytic Staphylococcus aureus. Prompt improvement in the general condition of the patient followed the administration of the antitoxin. The white blood count rose to 12,000 with 40 per cent segmented and 20 per cent non-segmented polymorphonuclear leucocytes. The temperature was practically normal by the fifteenth day. A severe, non-febrile urticaria developed on the twelfth day. The patient continued to improve and was discharged on the forty-second day with a chronic draining infection.

Case 54860. R. J., white female, age 9, was admitted to the hospital July 3, 1935, complaining of inability to straighten the right leg. Following a bruise in the right groin 2 weeks before admission, slight pain, malaise, and anorexia were noted which gradually increased. For 5 days before admission,

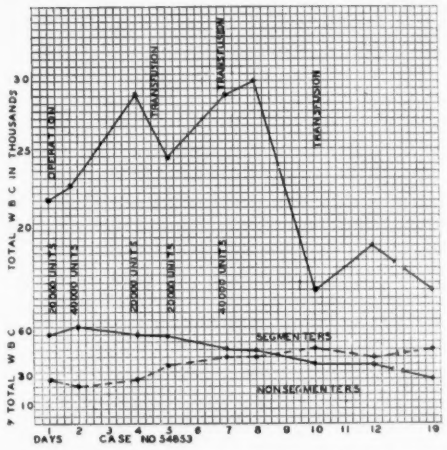

Fig. 2. Case 54853. Shows hemogram of a 12 year old negro boy with acute osteomyelitis and staphylococcemia. This patient had multiple foci of infection and required 140,000 units of antitoxin to produce a favorable hemogram.

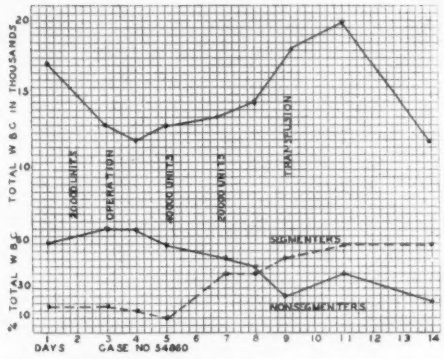

Fig. 3. Case 54860. Shows hemogram of a 9 year old white girl with acute osteomyelitis and staphylococcemia. This patient received about the average dosage of antitoxin (80,000 units). Note the favorable shift in the hemogram before transfusion.

there was severe pain in the right hip associated with nausea, vomiting, chills, and fever.

On examination she was found to be acutely ill, with increased heat, swelling, and tenderness in the region of the upper end of the femur. Excruciating pain was caused by motion of the right leg. She was given intramuscularly 35 cubic centimeters (20,000 P. international units) of staphylococcus antitoxin (Lederle). Her condition remained about the same during the second day. On the third day, the infection in the right hip was incised and drained by Dr. Randolph Jones. The blood cultures showed two colonies per cubic centimeter of hemolytic Staphylococcus aureus. Following the operation she was given 70 cubic centimeters (40,000 P. international units) of antitoxin. She continued to have chills and her temperature varied from 39 to 41 degrees C. so she was given another 70 cubic centimeters (40,000 P. international units) on the fourth day and 35 cubic centimeters (20,000 P. international units) on the fifth day. The blood picture showed a dramatic shift from 60 per cent non-segmented polymorphonuclear leucocytes and 15 per cent segmented leucocytes to 20 per cent non-segmented and 60 per cent segmented forms (Fig. 3). The patient began to improve and the organisms disappeared from the blood although the temperature continued to fluctuate from 37.5 to 39.5 degrees C. Thirty days later she still had a chronic osteomyelitis with some fever and is being actively immunized with staphylococcus toxoid.

Case 54853. R. J., negro boy, age 12, was admitted to the hospital July 3, 1935, complaining of pain and swelling in the right hip for 9 days. Following an injury to the right hip by a fall a diffuse swelling which extended down to the knee appeared the next day. Fever, tenderness, anorexia, and malaise gradually increased up to time of admission.

Examination revealed an acutely ill, negro boy crying with pain in the right leg. There was swelling, increased heat, and tenderness from the iliopectineal line to the knee of the right leg. There was also pain, swelling, and an increase in local heat over the middle toe of the left foot. He was given 35 cubic centimeters (20,000 P. international units) of staphylococcus (Lederle) intramuscularly and then taken to the operating room where Dr. H. Shiebel incised and drained the disease process in the right thigh. The temperature varied from 39 to 41 degrees C. and 70 cubic centimeters (40,000 P. international units) of antitoxin was given on the second day. The blood cultures showed per cubic centimeter of blood five colonies of hemolytic Staphylococcus aureus. On the third day the blood picture showed a marked improvement with a shift from 60 per cent non-segmented polymorphonuclear leucocytes and 20 per cent segmented leucocytes to 30 per cent non-segmented and 55 per cent segmented forms (Fig. 2).

He received 35 cubic centimeters (20,000 P. international units) of antitoxin on the third day and a transfusion of blood. The middle toe on the left foot was incised and drained. During the next 4 days he received five small transfusions and a total of 140 cubic centimeters (80,000 P. international units) of antitoxin. The hemoglobin which was 4 grams was raised to 7 grams by these transfusions. On the sixth day the patient developed marked edema of the scrotum and penis which was attributed to local lymphatic involvement although there was albumin in the urine and the blood chemistry studies showed a non-protein nitrogen of 120 milligrams per cent, and a reversal of the albumin globulin ratio. The temperature reached normal by the twenty-eighth day, and blood cultures have

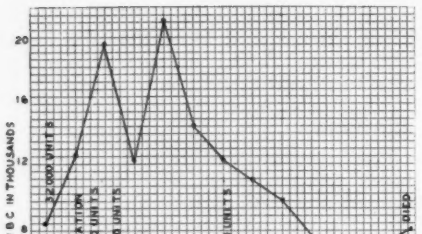

Fig. 4. Case 52981. Shows hemogram of a 12 year old white boy who died of acute osteomyelitis with staphylococcemia and pneumonia. Although he received 256,000 units, the hemogram remained unfavorable.

remained sterile. The osteomyelitis is in the chronic stage, but the urine still shows albumin and a few red blood cells, and the patient has a generalized edema which is subsiding.

CASE 52981. H. M. R., white male, age 12 years, was admitted to the hospital on May 24, 1935, with the complaint of pain in the left ankle and fever for 6 days; chills, nausea, and vomiting for 4 days. He was acutely ill with flushed face, mental disorientation and marked tenderness, swelling, redness, and increased heat over the lower end of the left tibia.

After a preliminary skin test he was given intramuscularly 40 cubic centimeters (32,000 P. international units) of staphylococcus antitoxin (Lederle). The following morning the site of the osteomyelitis was incised and drained by Dr. B. Raney. Blood stream cultures and cultures from the pus from the tibia were positive for hemolytic Staphylococcus aureus. He received intramuscularly 100 cubic centimeters (80,000 P. international units) of antitoxin on the second day, 200 cubic centimeters of citrated blood, and 100 cubic centimeters (80,000 P. international units) of antitoxin on the third day. The disease continued to progress and the temperature ranged from 39 to 41 degrees C. Substernal pain appeared on the fourth day and the roentgenograms showed a uniform consolidation in the right and left lower lobes. Repeated blood cultures showed per cubic centimeter twenty to thirty colonies of hemolytic Staphylococcus aureus. By the seventh day the patient was practically moribund. At this time 100 cubic centimeters (80,000 P. international units) of antitoxin was mixed with equal parts of saline and given intravenously over a period of 1 hour and 30 minutes. The patient went to sleep while the injection was being given. The temperature dropped to normal and remained within the normal limits for the next 8 hours, and then rapidly rose to the former range of 39 to 40 degrees C. Jaundice appeared on the fourth day and gradually increased presenting a direct Van den Bergh of 4.7 milligrams per cent on the ninth day. Although the percentage of segmented polymorphonuclear leucocytes increased immediately after the intravenous antitoxin, the total white count steadily dropped to 5,200 (Fig. 4) and the respirations ceased on the thirteenth day.

Necropsy findings: Acute osteomyelitis of the left tibia. Multiple abscesses of both lungs, heart, kidneys, anterior and posterior thoracic muscles. Periostitis of the right clavicle and the left third and fourth ribs anteriorly. Hemorrhagic myocarditis, gastritis, enteritis, and pyoarthritis of the right clavicular sternal joint.

SUMMARY

These children with acute osteomyelitis and staphylococcemia presented a picture of profound toxemia with chills, high fever, disproportionately high pulse rate, respiratory distress, and sometimes delirium. Our experience is in accord with that of Dolman (9) who maintains that the majority of symptoms are due to the *in vivo* production of staphylococcus toxin and not to the presence of staphylococci in the circulating blood. The administration of antitoxin in sufficient amounts relieves the general symptoms, although organisms persist for several days in the blood stream. The antitoxin is not directly bacteriocidal but has an indirect bacteriocidal action by neutralizing the circulating toxin and thus removing the inhibition of the normal phagocytic activity of the leucocytes. Our studies suggest that the mechanism is of major importance since those patients who lost toxic symptoms following administration of antitoxin, all showed an increase in the white blood cell count with a return to a more normal ratio of segmented to non-segmented polymorphonuclear leucocytes. The patients who died showed a progressive disproportion of non-segmented to segmented leucocytes. It is more than likely that the toxin which produces this change in the leucocytes is also damaging other cells in the body. Certainly the segmented non-segmented ratio seems to be a simple measure of the degree of toxemia and a convenient guide to the dose of antitoxin and frequency of its administration.

The dosage will vary with the severity of the disease, with the duration of the disease before treatment, and with the size of the patient. We have obtained good results with as little as 32,000 P. international units and as much as 160,000 units. Prompt and adequate surgical drainage of all foci is absolutely essential since this prevents the absorption of additional toxin. Multiple blood transfusions are also indicated.

Eleven of our patients were given antitoxin intramuscularly without general serum reaction, but practically all later developed serum sickness. In 1933 we administered antitoxin intravenously to two adult patients with staphylococcus infection, but no osteomyelitis. They both had severe serum shock. This corresponds to the experience of Dolman and Keith with the intravenous administration of antitoxin. We have always considered intravenous injections the ideal method of treatment if the danger of shock could be eliminated. Three recent patients have been treated intravenously with a highly refined and purified antitoxin, resulting in only a mild chill and slight febrile reaction. The clinical improvement was dramatic with a drop in temperature, a rise in segmented polymorphonuclear leucocytes, and a loss of general toxic symptoms.

CONCLUSIONS

1. The majority of the symptoms shown by children with acute osteomyelitis and staphylococcemia are due to *in vivo* production of toxin.

2. Commercial staphylococcus antitoxin will neutralize *in vivo* the exotoxins of heterogenous strains of staphylococci.

3. The segmented non-segmented ratio of the polymorphonuclear leucocytes is an indication of the severity of the toxemia and a convenient guide to the dose of antitoxin and frequency of administration.

4. Sixteen patients with acute osteomyelitis and staphylococcemia treated by prompt drainage and multiple blood transfusions resulted in 8 deaths and an equal number of recoveries.

5. Thirteen patients with the same type of infection treated by the same method supplemented by the administration of staphylococcus antitoxin resulted in 2 deaths and 11 recoveries.

BIBLIOGRAPHY

1. Bigger, J. W., Boland, C. R., and O'Meara, R. A. Q. New method of preparing staphylococcal hæmolysin. J. Path. & Bacteriol., 1927, 30: 271–277.
2. Idem. Production of staphylococcal hæmolysin with observations on its mode of action. J. Path. & Bacteriol., 1933, 36: 87–114.
3. Birch-Hirschfeld, L. Ueber die Wirksamkeit der Extrakte von auf Zellophanagar gezuchteten Staphylokokken. Ztschr. f. Immunitaetsforsch. u. exper. Therap., 1934, 81: 260–285.
4. Burky, E. L. Studies on cultures and broth filtrates of staphylococci; antitoxin content of rabbit serums immune to staphylococcus toxin and precipitin reactions of such serums. J. Immunol., 1933, 25: 419–437.
5. Burnet, F. M. Interactions of staphylococcus toxin, anatoxin and antitoxin. J. Path. & Bacteriol., 1931, 34: 471–492.
6. Combiesco, D., Istrati, G., and Combiesco, N. Recherches sur l'exotoxine staphylococcique. Compt. rend. Soc. de biol., 1933, 114: 292–294.
7. Connor, J. I., and McKie, M. Study of antihæmolytic titre of sera of man and animals following staphylococcal infection. J. Path. & Bacteriol., 1933, 37: 353–357.
8. Dolman, C. E. Pathogenic and antigenic properties of staphylococcus toxin. Canadian Pub. Health J., 1932, 23: 125–132.
9. Idem. Staphylococcus antitoxic serum in the treatment of acute staphylococcal infections and toxæmias. Canadian M. Ass. J., 1934, 30: 601.
10. Forssman, J. Studien ueber das Staphylolysin. Biochem. Ztschr., 1933, 265: 291–319.
11. Gross, H. (Marburg). Die Kulturfiltratstoffe der Staphylokokken und deren Beziehungen zueinander. Ztschr. f. Immunitaetsforsch. u. exper. Therap., 1931, 73: 14–26.
12. Idem. Ist eine geeignete Serumtherapie der Osteomyelitis moeglich und erfolgversprechend? Arch. f. klin. Chir., 1933, 175: 454–457.
13. Idem. Die Wertbestimmungsmethoden des antitoxischen Staphylokokkenserums. Ztschr. f. Immunitætsforsch. u. exper. Therap., 1933, 79: 163–170.
14. Idem. Ueber die Brauchbarkeit und den diagnostischen Wert der antistaphylolysinreaktion. Klin. Wchnschr., 1933, 12: 907–908.
15. Hartley, P., and Smith, M. L. A proposed international standard for staphylococcus antitoxin. Quart. Bull. Health Organ.; League of Nations, 1935, Jan.: 68–110.
16. Jamieson, H. C., and Powell, H. M. Immunology of staphylococcus toxin. Am. J. Hyg., 1934, 19: 246–253.
17. Joyner, A. L., Rigdon, R. H., and Hare, R. Effect of staphylococcus toxin on the white cells of the rabbit. Unpublished.
18. Keith, W. S. The clinical use of staphylococcus antitoxin and of toxoid. To be published J. Am. M. Ass.
19. Kraus, R., and Clairmont, P. Ueber Hamolysine und Antihamolysine. Wien. klin. Wchnschr., 1900, 13: 49.

20. KRAUS, R., and PRIBRAM, E. Ueber Staphylokokkentoxin und dessen Antitoxin. Wien. klin. Wchnschr., 1906, 19: 493.
21. NEISSER, M., and WECHSBERG, F. Ueber das Staphylotoxin. Ztschr. Hyg. u. Infektionskrankh., 1901, 36: 299.
22. NELIS, P. Contribution a l'etude de la toxine staphylococcique. Compt. rend. Soc. de biol., 1933, 113: 7.
23. NICOLLE, M., and CESARI, E. Etudes sur les staphylocoques dores. Ann. de l'Inst. Pasteur, 1914, 28: 213.
24. PANTON, P. N., and VALENTINE, F. C. O. Staphylococcal toxin. Lancet, 1932, 1: 506–508.
25. PANTON, P. N., VALENTINE, F. C. O., and DIX, V. W. Staphylococcal infection and antitoxin treatment. Lancet, 1931, 2: 1180–1183.
26. PARISH, H. J., and CLARK, W. H. M. Staphylococcal toxin and antitoxin. J. Path. & Bacteriol., 1932, 35: 251–258.
27. PARKER, J. T. Production of exotoxin by certain strains of Staphylococcus aureus. J. Exper. Med. 1924, 40: 761–772.
28. PARKER, J. T., and BANZHOF, E. J. Production of staphylococcus antitoxin in horses. J. Immunol., 1927, 13: 25–29.
29. PIKE, R. M. Depression of phagocytosis by products of staphylococci. J. Immunol., 1934, 26: 69–80.
30. RIGDON, R. H., JOYNER, A. L., and RICKETTS, E. T. Study of action of filtrable staphylococcal toxin on kidneys of normal rabbits. Am. J. Path., 1934, 10: 425–434.
31. VAN DE VELDE, H. Etude sur le mecanisme de la virulence du staphylocoque pyogene. Cellule, 1894, 10: 403.
32. WELD, J. T. P., and GUNTHER, A. Differentiation between certain toxic properties of filtrates of hemolytic Staphylococcus aureus. J. Exper. Med., 1931, 54: 315–322.

CYCLICAL CHANGES IN THE HUMAN VAGINAL MUCOSA

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IT was the physiologist, Ludwig, who enunciated the principle that changes in the function of body tissues are always associated with differences in structure. In the years which have followed the formulation of this thesis, students of morphology and physiology have found abundant evidence supporting it. The recent discoveries concerning the reproductive physiology of the female have been associated continuously with studies which reveal alterations in the finer structure of the generative organs in response to physiological stimuli. It has been demonstrated that the tissues of the uterine and tubal mucosa as well as those of the ovarian cortex and the adenohypophysis vary as regards their cellular content and arrangement so that they present histological pictures characteristic of the different stages of the ovarian cycle.

The mucosa of the fundus of the uterus and that of the oviduct have such a definite cellular response to the pituitary and ovarian cycles that one is able to diagnose from them the status of structures in the ovary with a great degree of certainty. It might be logical to assume, therefore, that other portions of the Muellerian duct, such as the cervix and vagina, might show evidence of rhythmic histological change in an analogous manner. Thus far, no study of the cervical epithelium of the woman from this point of view has appeared, although Hartmann and Olbers (1931) have drawn attention to the very definite cycle in the cervix of the guinea pig. On the other hand the search for a histological cycle in the vagina has engaged the attention of many workers, but unfortunately a wide divergence of opinion has resulted as a brief historical résumé will show.

Morau, in 1889, observed that the vaginal epithelium of rodents underwent structural changes under the influence of estrus and ovulation. These observations were confirmed by de Retterer, in 1892, and Lataste, in 1893. Their significance was not sensed, however, until Stockard and Papanicolaou in 1917 again called attention to them and unmistakably correlated the cellular response of the guinea pig vagina to that in the ovary. These observers went further and demonstrated that smears made from the vaginal fluid and cell content of the vagina also revealed variations which were specific with regard to the phases of the ovarian cycle.

Stieve, in 1925, contributed his first study of the human vaginal epithelium from the point of view of cyclic change. Although he studied the mucosa of only two women, one of whom was sterile and possessed of an infantile uterus, he made the sweeping statement that there are no essential cyclical changes in the vaginal epithelium other than moderate hypertrophy and hyperplasia of the squamous cells, leucocytosis, and hyperemia during the premenstrual phase.

The year 1927 brought forth several studies of the human vagina. Dierks and Puccioni working independently, reported investigations in which the former observed 30 women and the latter, 20, all of whom were menstruating normally. Both agreed that there were definite rhythmic variations of the vaginal epithelium which could be correlated to the menstrual cycle. Dierks divided the epithelium into three layers, a functionalis or outer layer, an intra-epithelial hyalinized layer, and a basalis. The basalis, he concluded, is refractory, showing no change, while all of the functionalis and part of the zone of cornification are shed during menstruation. Puccioni differentiated between an intermenstrual, a premenstrual, and a menstrual phase of the vaginal cycle. In the first of these, he thought the regeneration of the tissue to take place, while he considered the premenstruum to be characterized by strong proliferation, marked hyperemia, and the commencement of shedding. The latter he described as continuing during menstruation and then being followed by a phase of rest. Both of these observers based their

work upon a single biopsy from each patient taken from any convenient location, which may be worthy of note in view of Stieve's later work, as well as that which we shall present. In the same year Fraenkel and Fels corroborated most of Dierks' findings concerning the vaginal epithelium but were unable to correlate them with the ovarian cycle. We have no details as to their material or methods.

Since 1928 a great many contributions have been made to the subject with a majority of the observers unable to confirm the occurrence of the vaginal cycle. Stemshorn, Lindemann, Nuernberger, Lahm, Fels, Heynemann, Gisbertz, Kuechens, Walther, Keller, and Schiller are among those who, for the most part, repudiated Dierks' work. On the other hand, Adler, Pankow, Esch, Dyroff, Davanzo, Vinos and Geist, with Smith and Brunner, confirmed the existence of a vaginal cycle although all of them, except Vinos, did so with definite reservations. Stieve again studied the problem in 1931 and wrote two additional articles in which he adhered to the views he expressed in 1925. In addition he found he could attribute no importance to the "zone of cornification" as described by Dierks, pointing out that it is inconstant, being found in some locations and not in others, or that it can be found in any phase of the menstrual cycle, as well as during pregnancy, before puberty, and after the menopause. Its presence, he felt, is dependent upon mechanical factors, certainly not upon endocrine relationships. Furthermore, he described similar cornifications in other parts of the body such as the buccal mucosa and the esophagus in male, as well as female, subjects.

In 1935, Davis and Hartmann studied the vaginal mucosa of the rhesus monkey by making biopsies from each animal at the same level of the vagina at weekly intervals. They were convinced that in this animal the vaginal epithelium responds in characteristic fashion to stimuli which coincide with the ovarian phases.

This brief review of the literature gives abundant evidence that the problem of rhythmic variation in the human vagina, though much studied, is far from being established. We believe that this diversity of opinion has arisen from the application of faulty methods, in that none of these observers of human material obtained any considerable number of biopsies from the same patient or observed the precaution of focusing their observations upon a definite location in the vagina. As Stieve and Pankow pointed out, there frequently are wide variations between the upper and lower portions of the same vagina at the same time. We feel, therefore, that there is need for further study of the subject and are particularly stimulated because of the recent demonstration of Papanicolaou proving that smear preparations of the human vagina have a characteristic variation in their cellular content which can be considered as specific for the various phases of the menstrual cycle. Inasmuch as the cells he describes in his studies concern leucocytes and young or old squamous epithelial cells principally, it would seem almost certain that the variations as represented in smears of these cells must arise as a result of very definite fluctuations in the histological character of the vaginal mucosa.

MATERIAL AND TECHNIQUE

This study of the human vaginal mucosa is based upon specimens taken from 29 normally menstruating women who had no gynecological or endocrine condition which might vitiate the observations in so far as could be ascertained. In 12 of these women it was possible to secure 4 or more vaginal biopsies at weekly intervals so that in them a complete menstrual cycle is represented. From the 17 remaining patients, either a lesser number of specimens were secured or intervals longer than a week elapsed between the taking of biopsies. The conclusions of the study are based principally upon the former group, while the second has been used as additional evidence only when time sequence or the lack of frequent observation did not seem important to the point under consideration. Although the patients were selected because they menstruated normally and because they were thought to be free of disease, a few developed some menstrual irregularity while under observation, whether as a result

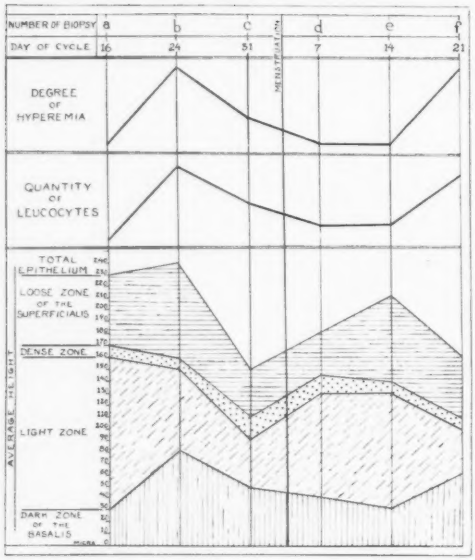
TABLE I.—TABULATION OF MEASUREMENTS—CASE 12*

Number of biopsy		a	b	c	d	e	f
Day of cycle		16th	24th	31st	7th	14th	21st
Total epithelium—	Maximal height	300	400	200	370	400	290
	Minimal height	150	200	60	60	110	60
	Average height	230	240	150	180	210	160
Superficialis—	Maximal height	110	180	150	70	140	110
	Minimal height	20	30	20	3	16	15
	Average height	70	90	60	50	80	60
Basalis—	Maximal height	220	220	370	340	340	150
	Minimal height	100	20	20	30	20	15
	Average height	160	150	90	130	130	100
Loose zone—	Maximal height	110	180	80	70	140	110
	Minimal height	0	0	0	3	0	0
	Average height	60	80	40	35	70	50
Dense zone—	Maximal height	40	50	30	40	20	20
	Minimal height	0	0	0	0	0	0
	Average height	10	10	20	15	10	10
Light zone—	Maximal height	230	110	80	220	300	70
	Minimal height	20	0	0	0	10	0
	Average height	130	70	40	90	100	40
	Number of cell layers	6–10	0–8	0–5	0–11	1–20	1–6
	Average height of a single layer	16	14	14	15	14	14
Dark zone—	Maximal height	60	180	80	80	60	110
	Minimal height	15	40	20	10	10	15
	Average height	30	80	50	40	30	60
	Number of cell layers	2–6	4–16	3–9	1–7	1–7	3–12
	Average height of a single layer	8	7	8	9	8	7
Diameters of the larger cells of the light zone		60/18	40/18	30/18	40/18	30/11	30/11
Number of mitoses		0	0	0	0	0	0
Quantity of leucocytes—	Basalis	+	+++++	++++	+++	+++	+++++
	Tunica propria	+	+++	+++	++	++	++
Hyperemia		None	Marked	Slight	None	None	Marked
Density of the tunica propria		Medium	Medium	Medium	Medium	Medium	Medium

*An example of the method of measurement used in analyzing the various biopsy specimens. This woman had a menstrual cycle of 31 days so that 6 biopsies were necessary to complete the cycle. All measurements are in micra. A similar table was made for each of the 11 other women whose vaginas were observed in this study.

of the biopsies or not we are unable to decide. These minor irregularities have been taken into consideration, when they occurred, and the data from the case rejected or retained depending upon whether or not subsequent cycles were normal.

All biopsies were taken at the same level of the vagina. The sites chosen were on the lateral walls, in the middle of the upper third of the vagina. The specimens were taken with an ordinary tissue rongeur and nearly always by the same operator. The procedure was painless and bleeding usually insignificant. The specimen, a round piece of tissue about 6 millimeters in diameter, was immediately placed in Bouin's solution for fixation



Graph 1. A graphic representation of the data from Table I in which the various elements are plotted. This therefore portrays the fluctuations in the various elements of the vaginal mucosa at various moments in the menstrual cycle. A similar graph was made for each of the other 11 women whose vaginas were observed.

and embedded in paraffin. Sections were cut 5 micra in thickness and were stained in hematoxylin and eosin. A considerable number were also stained by the trichrome method of Masson. In this way several hundred sections were prepared from the 96 biopsy specimens obtained.

METHOD OF STUDY

In evaluating the material several different cell counts and measurements have been made with regard to the various zones (Table I) while for purposes of clarity the different strata have been classified according to the following schema:

Superficialis
- Loose zone (Dierks' "functionalis")
- Dense zone (Dierks' zone of cornification or zone of densification of other authors)

Basalis
- Light zone
- Dark zone

(Based on reaction to hematoxylin)

Lamina propria

The cells of these successive layers of the epithelium are of different ages. In the bottom layer are the primitive cells, which proliferate and give rise to immature cells forming the dark zone, so called because of their dense staining reaction. These then mature progressively as they ascend in the epithelium. At the same time, the basophilia of their nuclei and cytoplasm decreases markedly so that they come to form the light zone of the basalis. Subsequently, the cells degenerate and cornify, their nuclei grow pyknotic, and they then form the superficialis. In the end they are shed as though pushed out by the new cells coming from below. As we shall show later, these periods of growth are rhythmic, and it might therefore seem that desquamation should be more or less periodic as well; however, thus far, we have been unable to substantiate such a deduction definitely.

Table I gives an example of the measurements which were made for each of the twelve subjects studied. The measurements were then charted graphically as in Graph 1 and from them deductions became possible.

Comparison of the graphs thus obtained reveals the fact that the vaginal mucosa has a growth rhythm as evidenced principally by periods of proliferative activity in the dark zone of the basalis alternating with periods of quiescence in which no evidences of growth may be seen. No consistent variations could be found in the other layers of the epithelium.

GENERAL DESCRIPTION OF THE VAGINAL MUCOSA DURING THE INACTIVE PHASE

The connective tissue of the tunica propria contains lymphatics and blood vessels. In its upper portions a small number of leucocytes are usually seen, while just beneath the epithelial margin is a thin, poorly differentiated fibrous sheet known as the lamina propria. The basal layer of the epithelium forms an undulating line with small papillæ which project downward into the tunica propria.

The basal layer of cells in the dark zone is very regular in size and disposition. Their nuclei are large, stain deeply with hematoxylin, and almost completely fill the cell. The nucleus is oval in shape, and its greatest diam-

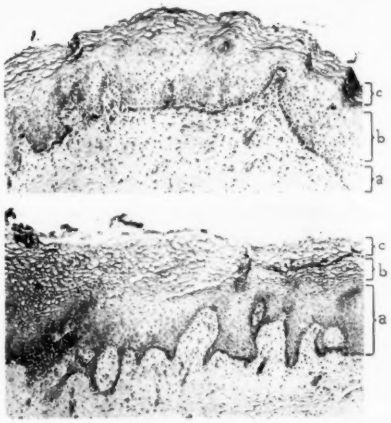


Fig. 1. Photomicrographs of biopsy specimens from the same vagina. The upper one was removed on the fifteenth day of the cycle and is in the inactive phase. The lower picture represents the proliferative phase and was removed on the fifth day of the cycle. *a*, Basalis, dark zone; *b*, light zone of basalis; *c*, superficialis. The lower picture shows marked proliferation and increased height of the dark zone as compared to the upper one. ×100.

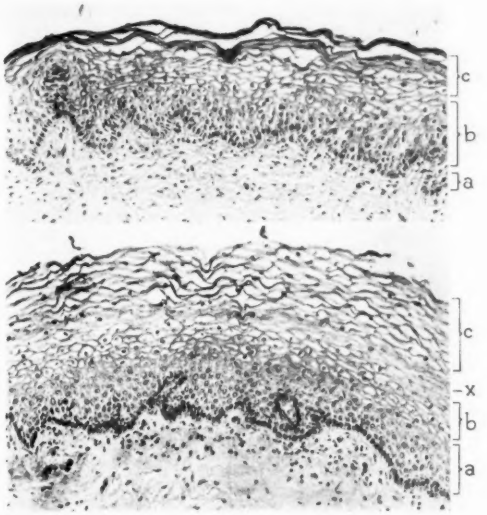


Fig. 2. Upper, Inactive phase. Biopsy removed on the tenth day of cycle. Lower, Proliferation of basalis in same patient, biopsy removed on the seventeenth day. *a*, Basalis, dark zone; *b*, basalis light zone; *c*, superficialis. *x*, Dierks' "zone of cornification." ×90.

eter always lies perpendicular to the lamina propria. This layer forms a definite dark ribbon of cells at the base of the epithelium and is frequently referred to as the stratum germinativum.

Superimposed on this single layer of the germinativum are four or five layers of larger cells, which are more irregular in disposition. The orientation of their nuclei is not uniform, but the nucleus itself presents the same appearance as those of the bottom layer. As the cells are larger, somewhat older, and not so closely packed, their affinity toward the basic stain is generally less marked. These together with the germinal layer have been designated as the dark zone of the basalis because they stain intensely with the basic hematoxylin dye.

In the light zone of the basalis, the cells are markedly larger than those of the dark zone and increase in size as the upper layers are reached. The outline of the cell has changed from oval or octagonal to a flat spindle contour. The cell membranes are more apparent and the protoplasm is vacuolated. The nuclei show evidences of degeneration which become more marked as the upper layers of the light zone are approached. They stain less deeply with hematoxylin and their chromatin is shrunken to form a small, irregular spot in the center of the large nucleus. This transition from the lower to the upper layers is usually progressive, and the cellular changes are interpreted as depicting the gradual death of the cells.

In the superficialis the process of stratification and cornification takes place. There is a very abrupt change from the basalis to the superficialis. The cells of the latter take almost none of the hematoxylin stain and are, for the most part, quite loose in their arrangement. Occasional areas of dense or compact arrangement are frequently observed and when present may be in any part of the superficialis. It is this latter occurrence which Dierks and others have alluded to as "intra-epithelial zone of cornification" (Fig. 2).

Dierks considered that the appearance of his "intra-epithelial zone of cornification" was a symbol of ovarian hormone effect and that it was characteristic of the premenstrual phase. As has been pointed out in the discussion of the literature, many authors have

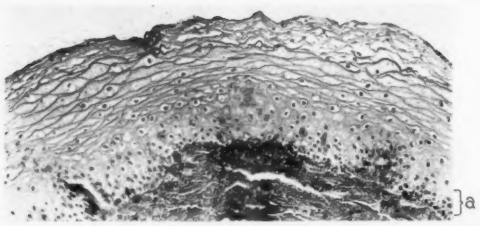


Fig. 3. Patient 12. Figures 3 to 8, inclusive, represent one series of biopsies of the study. The data of Graph 1 and Table I were obtained from these same biopsies. Sixteenth day of cycle. Inactive phase. Dark zone, *a*, is low. ×90.

found this histological picture in the vaginal epithelium of individuals previous to puberty and after the menopause. Stieve has also shown that such cornification may occur in the buccal and esophageal mucosa. All this evidence seems to indicate a lack of specificity in this epithelial reaction. On the other hand, there is no agreement among other authors that this represents real cornification. One of this group, Stemshorn, therefore, proposes the use of the term "area of densification."

DESCRIPTION OF THE VAGINAL EPITHELIUM DURING THE PROLIFERATIVE PHASE

As the outstanding and only constant histological variation possessed of a rhythmic nature, we have observed a proliferative phase which usually begins in the premenstruum. This phase is characterized by a proliferation of the young cells in the dark zone of the basalis and results in enlargement of the papillæ both in breadth and depth so that there is marked increase in irregularity of the

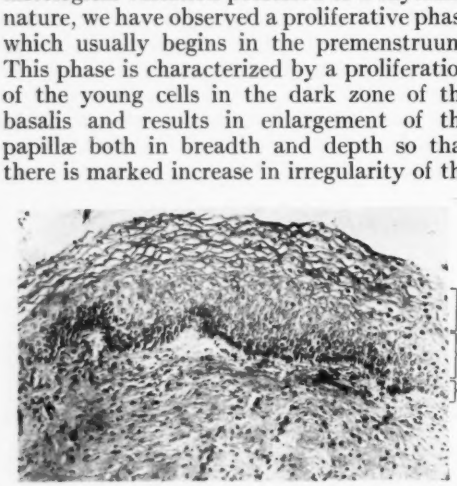


Fig. 5. Patient 12. Thirty-first day of cycle. Proliferative phase is regressive. *a*, Dark zone, basalis; *b*, light zone, basalis; *c*, superficialis. ×90.

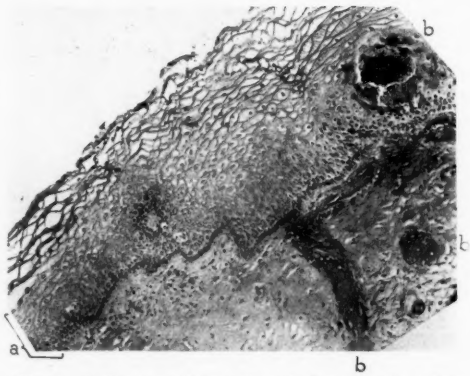


Fig. 4. Patient 12. Twenty-fourth day of cycle. Proliferative phase. Dark zone of basalis hyperplastic, *a;* congested blood vessels, *b*. ×90.

margin between the basalis and lamina propria. Mitoses are only rarely observed. At the same time there is a marked increase in height of this zone. The growth period may or may not be accompanied by changes in the more peripheral layers. We have been unable to discern any constancy in reaction above the dark zone of the basalis. However, more or less synchronous with the proliferative activity, we have observed dilatation and increased numbers of blood capillaries (Fig. 4) associated with an infiltration of leucocytes which invade the tunica propria and the epithelium. Such leucocytes never disappear completely during any phase of the menstrual cycle, but their numbers undergo variation, with a tendency for the maximum to occur at the period of proliferation.

Unfortunately, from a theoretical point of view, the incidence of the proliferative phase in the vagina is somewhat variable with respect to the menses. However, in the majority of our subjects it occurred between the twenty-first and the seventh days of the cycle, thus seeming to coincide roughly with the menstrual period. The proliferative phase covers several days, beginning and ending gradually. The biopsies do not always coincide with its maximum development, sometimes showing the ascending process while others show it on the wane. If one were to demonstrate the beginning, maximum development, and end of the process, it would

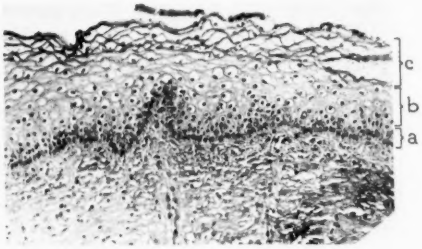


Fig. 6. Patient 12. Seventh day of cycle. Inactive phase. *a*, Dark zone; *b*, light zone; *c*, superficialis. ×90.

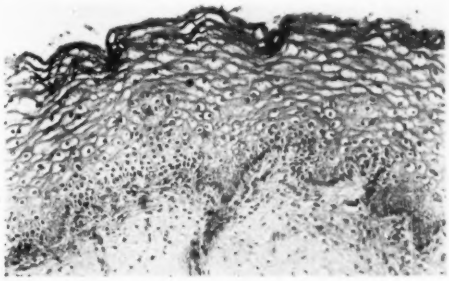


Fig. 7. Patient 12. Fourteenth day of cycle—also inactive phase. ×90.

probably be necessary to take daily specimens, which, from the practical point of view, is impossible in the human subject. Several of our patients exhibited the proliferative phase as a purely menstrual phenomenon while others began premenstrually, continued during menstruation, and on into the postmenstruum.

Some authors have described hyperemia of the vaginal mucosa just before and during menstruation. Our observations show that the hyperemia is not related to menstruation but to the proliferative phase. In those subjects in which the proliferative phase was terminated before menstruation, there was no observable hyperemia during the menses. On the other hand, in those patients in whom the proliferative phase extended into postmenstruum, hyperemia was definite.

Numerous biopsies made from the vaginas of pregnant women have not revealed the proliferative phase as we have described it. On the other hand, the quiescent appearance of the inactive phase is not seen. It would seem that during pregnancy the renewal of the vaginal epithelium occurs continuously instead of periodically as in the non-gravid state. The histological picture in all stages of pregnancy might be characterized as subproliferative in type.

DISCUSSION OF CONTROVERSIAL POINTS

Our observations concerning the dense zone of the superficialis (zone of cornification) do not confirm the descriptions of Dierks, Adler, Davanzo, and others. This phenomenon, when observable, presents marked variations of height and appearance, not only as between patients and the various biopsies from the same patient, but also with reference to different portions of a single microscopic preparation. It is impossible for us to substantiate anything resembling a regular evolution of this zone which might be correlated with the menstrual cycle.

In the loose zone of the superficialis, our observations, though not quite so categorically negative, are still inconsistent with the descriptions of these authors, who saw variations in height corresponding to the various phases of menstruation. In some instances we found that this zone was high in the premenstruum and low or nearly absent after the menses. However, quite the contrary was just as frequently seen. The variations in this respect even on a single microscopic slide were often marked and served to make comparisons difficult. However, we conclude that in most cases the variations of the superficialis seem to be without relation to the phase of the menstrual cycle. The same may be stated for the variations in the total height of the epithelium.

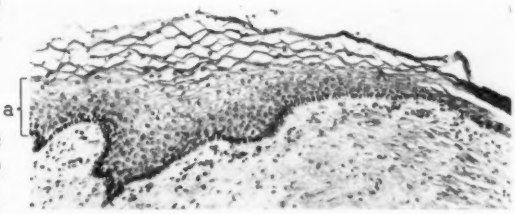


Fig. 8. Patient 12. Twenty-first day of cycle. Beginning of proliferative phase. Whole basalis occupied by uniformly staining dark cells. ×90.

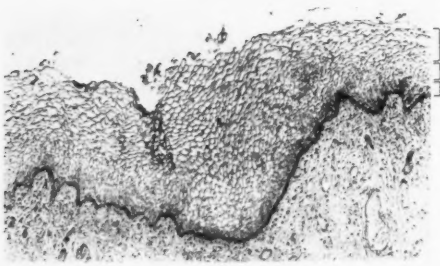


Fig. 9. Vaginal mucosa from fourth month of pregnancy. One of many biopsies all of which show same cellular relationships. *a*, Dark zone of basalis; *b*, light zone of basalis; *c*, superficialis. This status is maintained practically throughout pregnancy. ×50.

It seems difficult, therefore, if not impossible, to base the study of the "vaginal cycle" on the variations of the superficial zones, because they may be influenced by any one of several extraneous factors, such as coitus, the douche, etc. This probably explains the contradictory conclusions reached by the various authors. We conclude that there may be rhythmic exfoliation of the superficialis. Indeed, it would seem highly probable that this should occur in association with the periodic proliferative activity of the basal layer; however, we have not succeeded in demonstrating this sort of response. We feel that repeated frequent biopsies from normally menstruating virgins would be a more ideal and conclusive material upon which to base the study of the superficialis. The material of this study, however, seemed adequate for a study of the deeper placed layers of the vaginal epithelium and apparently justifies the following conclusions.

CONCLUSIONS

1. In the histological variations of the human vaginal mucosa, there is a definite rhythm which it is possible to correlate with menstruation and hence with the ovarian cycle.

2. This cellular response is characterized by proliferation on the part of the stratum germinativum with increase in the number of young epithelial cells in the basophilic zone of the epithelium. This response is associated with occasional mitoses and very definite leucocytosis and hyperemia.

3. The proliferative phase appears in the premenstruum, lasts 6 or 7 days and is either completed premenstrually or extends into the menstrual phase and occasionally into the postmenstruum. It has not been observed between the seventh and twenty-first days of the cycle. Between the proliferative phases the epithelium is quiescent.

4. Such alternation between proliferative and inactive phases has not been demonstrable by us in pregnancy, which seems to indicate that the rhythm of the vagina is related to the ovarian cycle.

5. We have been unable to correlate changes in the superficial and intra-epithelial layers of the vaginal mucosa with the menstrual cycle. According to our observations they are quite arrhythmic.

BIBLIOGRAPHY

1. Adler, K. Die Veraenderungen des Scheidenepithels waehrend des Menstruationszyklus und der Gestationsperiode. Arch. f. Gynaek., 1928, 134: 504–518.
2. Davanzo, I. Le modificazioni dell'epithelio vaginale della donna durante il ciclo menstruale. Riv. ital. di ginec., 1931, 13: 50–63.
3. Davis, M. E., and Hartmann, C. G. Changes in vaginal epithelium during pregnancy in relation to the vaginal cycle. J. Am. M. Ass., 1935, 104: 279–285.
4. Dierks, K. Der normale mensuelle Zyklus der menschlichen Vaginalschleimhaut. Arch. f. Gynaek., 1927, 130: 46–69.
5. Idem. Diskussionbemerkungen zu den Vortrag von Pankow (b). Zentralbl. f. Gynaek., 1928, 52: 2778–2780.
6. Idem. Experimentelle Untersuchungen an menschlicher Vaginal Schleimhaut. Arch. f. Gynaek., 1929, 138: 111–130.
7. Idem. Zur Frage des mensuellen Zyklus der menschlichen Vagina. Zentralbl. f. Gynaek., 1930, 54: 1882–1883.
8. Dierks, K., and Muenster, C. Polarisationsoptische Studien am menschlichen Vaginalepithel. Arch. f. Gynaek., 1932, 152, 1–12.
9. Dyroff, R. Diskussionsbemerkung zu dem Vortrag von Pankow (b). Zentralbl. f. Gynaek., 1928, 52: 2780–2781.
10. Esch. Diskussionsbemerkung zu dem Vortrag von Pankow (b). Zentralbl. f. Gynaek., 1928, 52: 2780.
11. Fels, E. Diskussionsbemerkung zu dem Vortrag von Pankow (b). Zentralbl. f. Gynaek., 1928, 52: 2778.
12. Fraenkel, L., and Fels, E. Deutsche med. Wchnschr., 1927, p. 2157.
13. Geist, S. H. Cyclical changes in vaginal mucous membrane. Surg., Gynec. & Obst., 1930, 51: 848–851.
14. Gisbertz, H. Zur Frage der periodischen Veraenderungen des menschlichen Scheidenschleimhautepithels. Arch. f. Gynaek., 1929, 136: 362–378.

15. HARTMANN, H., and OLBERS, H. Die zyklische Veraenderungen des Cerixepithels beim Meerschweinchen. Zentralbl. f. Gynaek., 1931, 155: 1314–1319.
16. HEYNEMANN, T. Diskussionsbemerkung zu dem Vortrag von Pankow. Zentralbl. f. Gynaek., 1928, 52: 2780.
17. KELLER, F. Ueber dem Menstruationszyklus der menschlichen Scheide. Zentralbl. f. Gynaek., 1930, 54: 641-654.
18. KUECHENS, H. Zur Frage der zyklischen Veraenderungen der Mamma und des menschlichen Scheidenepithels. Ztschr. f. Geburtsh. u. Gynaek., 1929, 96: 55–76.
19. LAHM, W. Diskussionsbemerkungen zu dem Vortrag von Nuernberger. Zentralbl. f. Gynaek., 1928, 52: 2685.
20. LATASTE. Transformation périodique de l'épithélium du vagin des rongeurs (rhythme vaginal). Compt. rend. Soc. de biol. 9 ème série, 1892, pp. 765–769.
21. Idem. Rythme vaginal des mammifères. Compt. rend. Soc. de biol. 9 ème série, 1893, pp. 135–146.
22. LINDEMANN, R. Zur Frage der cyklischen Veraenderungen der menschlischen Scheide. Jahrb. f. morphol. u. mikroskop. Anat.; 2. Abt., Ztschr. f. mikr.-anat. Forsch., 1928, 13: 373–387.
23. MORAU, H. Des transformations épithéliales de la muqueuse du vagin de quelques rongeurs. J. de l'anat. et physiol., 1889, 25: 277–297.
24. NUERNBERGER. Ueber den menstruellen Zyklus der Scheidenschleimhaut. Zentralbl. f. Gynaek., 1928, 52: 2685.
25. PANKOW, O. Der Menstruationszyklus der menschlichen Scheide. Zentralbl. f. Gynaek., 1928, 52: 2475–2477, 2777–2778.
26. PAPANICOLAOU, G. N. The sexual cycle in the human female as revealed by vaginal smears. Am. J. Anat., 1933, 52: 519–637.
27. PUCCIONI, L. Modificazioni istologiche della vagina della donna in rapporto con de varie fasi del ciclo funzionale dell'ovaio. Riv. ital. di ginec., 1927, 6: 544–556.
28. RETTERER, E. DE. Sur la morphologie et l'évolution de l'épithélium du vagin des mammifères. Compt. rend. Soc. de biol., 1892, 44: 101–107; Evolution de l'épithélium du vagin. pp. 566–568.
29. SCHILLER, W. Prosoplastische Veraenderungen des Portioepithels und ihre Beziehungen zum sog. Vaginalzyklus und zum Carcinombildung. Arch. f. Gynaek., 1934, 155: 415–442.
30. SMITH, B. G. Histological changes in the epithelium of the human vagina correlated with the menstrual cycle. Anat. Rec., 1929, 43: 317–343.
31. SMITH, B. G., and BRUNNER, E. K. Structure of human vaginal mucosa in relation to the menstrual cycle and pregnancy. Am. J. Anat., 1934, 54: 27–85.
32. STEMSHORN. Zur Frage des mensuellen Zyklus der menschlichen Vaginalschleimhaut. Zentralbl. f. Gynaek., 1928, 52: 2387–2392.
33. STIEVE, H. Das Schwangerschaftwachstum und die Geburtserweiterung der menschlichen Scheide. Ztschr. f. mikros.-anat. Forsch., 1925, 3: 307–366.
34. Idem. Verhornungserscheinungen im Epithel der menschlichen Speiseroehren und Scheidenschleimhaut. Ztschr. f. mikros.-anat. Forsch., 1931, 24: 213.
35. Idem. Ueber angebliche zyklische Veraenderungen des Scheidenepithels. Zentralbl. f. Gynaek., 1931, 55: 194–201.
36. VINOS, A. R. Sobre ciclo menstrual de mucosa vaginal humana. Rev. españ. obstetr., 1930, No. 169.
37. Idem. Weitere Untersuchungen zur Frage des Zyklus der menschlichen Vaginalschleimhaut. Arch. f. Gynaek., 1932, 148: 351–359.
38. WALTER, A. Gibt es zyklische Veraenderungen in der weiblichen Vaginalschleimhaut. Zentralbl. f. Gynaek., 1929, 53: 459–461.

A HISTOLOGICAL STUDY IN TWENTY-FOUR CASES OF RETAINED TESTES IN THE ADULT

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THE work of Moore (1, 2, 3, 4), Wangensteen, and others has shown that, in animals, the development of the testis depends very much upon its occupying a normal position in the scrotum. Although there is little evidence upon the point other than that derived from experimental studies on animals, it seems fairly certain that these observations ought to be translated into action in the treatment of the cryptorchid. It is now generally recognized that, in children, the testis must be made to lie in a wholly normal position at the bottom of the scrotum if the best opportunity for proper development is to be obtained. On the other hand, much difference of opinion still exists as to the proper treatment of the adult cryptorchid.

The experimental evidence at least suggests that the abnormally placed testis, if allowed to go into adult life in its malposition, may have been so thoroughly damaged that no regenerative process can be expected. Opposed to this are the frequent reports in isolated cases of the histological examination of the retained adult testis showing in some areas almost normal tubules and in others tubules which might conceivably show regeneration. For example, de Winiwarter (6, 7), examining two specimens of undescended testes, obtained, respectively, from patients of 23 and 40 years of age, expressed the opinion that the epithelium of the tubules was sufficiently preserved so that the possibility of regeneration to a normal condition could not properly be denied.

In our series we were concerned with the question of whether the degeneration shown in these retained testes was in general progressive, so that in the earlier decades the state of the epithelium would be such as to suggest the possibility of regeneration if placed under normal conditions, and whether in the later decades the degeneration had gone so far as to constitute practically complete atrophy.

We were also concerned with the still disputed question of the frequency of malignant disease developing in the abnormally placed testis. The weight of opinion appears to favor strongly the view that such malignant processes are importantly more common in the retained testis. In none of the patients with whom we were concerned did the testes, which were removed practically always in order to facilitate the cure of a hernia, show any gross evidence of malignant change. In none of them was the possibility of cancer entertained by the surgeon at the time of operation, but in 3 cases evidence of malignant disease was found by us.

ABSTRACT OF HISTOLOGICAL FINDINGS

No specimens were included in which the patient had not passed puberty.

Second decade. CASE 1. The patient was white, single, and 18 years of age. The testis was in the right inguinal canal. On microscopic examination only remnants of testicular tissue were seen, showing atrophic tubules with a very faint basement membrane. No germinal epithelium was found.

CASE 2. The patient was single, white, and 19 years of age. The testis was at the external ring. On microscopic examination the tunica albuginea was not abnormally thickened. The basement membrane of the seminiferous tubules was thick with slight atrophy of the germinal epithelium. An inflammatory stroma was noted, with increase in the fibrous connective tissue (Fig. 1).

In the first case only remnants of testicular tissue were seen, and it should be remembered that this was in an 18 year old boy. It is very doubtful whether this testis, if placed in the scrotum, would ever have developed a mature germinal epithelium.

In the second case the patient was 1 year older, and yet the testis was much larger. It is to be noted that there was very slight atrophy of the germinal epithelium. We do not think that anyone would doubt that this testis might develop a normal tubular epithelium if it had been placed in its normal position.

Third decade. CASE 3. The patient was white, single, and 20 years of age. The testis was in the right inguinal canal. On microscopic examination the tunica albuginea was found to be thickened, as was the basement membrane of the tubules. The germinal epithelium was slightly atrophied. The interstitial cells were not prominent.

CASE 4. The patient was white, single, and 21 years of age. The testis was in the left inguinal canal. On microscopic examination the tunica albuginea was found to be not abnormally thickened, and very few interstitial cells were seen. There was a thick basement membrane of the tubules. Most of the tubules showed no atrophy of the germinal epithelium, although a few of the tubules were devoid of epithelium. Just beneath the tunica albuginea was an early cancerous lesion. This lesion, in the opinions of three pathologists, was adenocarcinoma, grade 1 (Fig. 2).

CASE 5. The patient was white, single, and 22 years of age. The testis was in the right inguinal canal. On microscopic examination the interstitial cells were found to be diminished in number. There was partial atrophy and reduction in caliber of the tubules. An occasional tubule was hyalinized.

CASE 6. The patient was white, married, and 23 years of age. The testis was in the left inguinal canal. On microscopic examination the tunica albuginea was thick, as was the basement membrane of the tubules. The tubules were partially atrophic, and only a few interstitial cells were seen (Fig. 3).

CASE 7. The patient was white and 27 years of age. The testis was at the left external inguinal ring. On microscopic examination the tunica albuginea was thick, as was the basement membrane of the tubules. In areas the tubules were atrophied. Just beneath the tunica albuginea was a small cir-

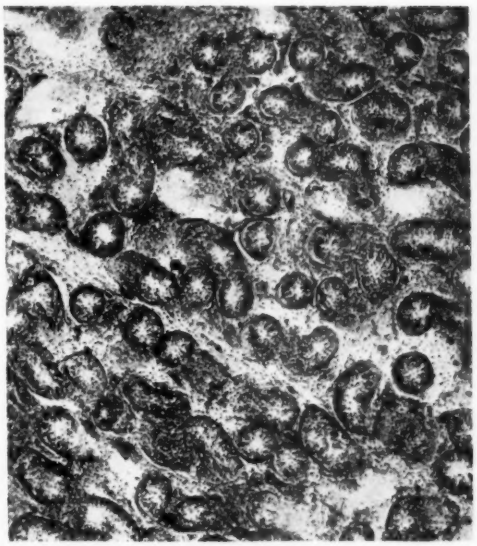

Fig. 1. Slight atrophy of the tubular epithelium with accentuation of the basement membrane. ×50.

Fig. 2. Adenocarcinoma, grade 1. Adjacent tubules show thickened basement membrane and normal germinal epithelium. The interstitial cells are not prominent. ×75.

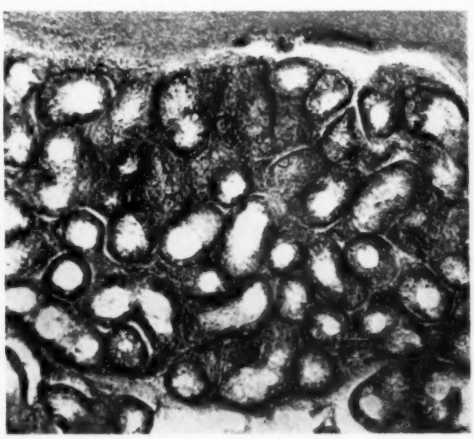

Fig. 3. The tubules adjacent to the tunica albuginea are shown with a thickened basement membrane and atrophic tubular epithelium. ×37.

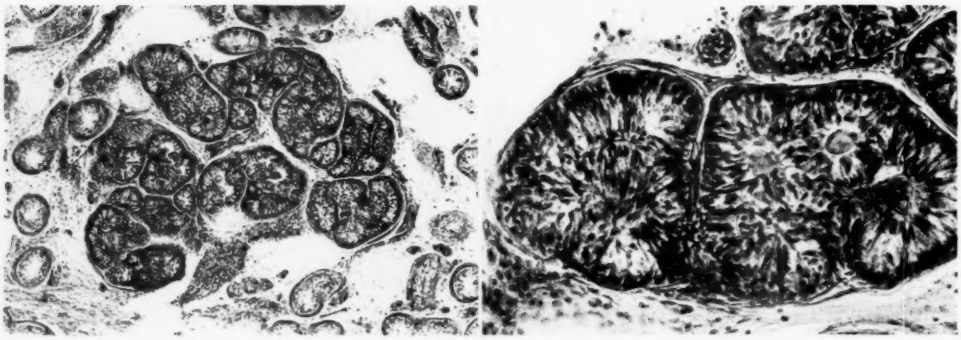

Fig. 4. Adenocarcinoma, grade 1, in a small nest of tubules. Surrounding this are tubules which show only slight atrophy. a, left, ×37; b, ×75.

cumscribed cancerous lesion. Scattered throughout the sections were tubules which showed this same lesion. This early cancerous lesion was called adenocarcinoma, grade 1, and in this diagnosis three pathologists concurred (Fig. 4).

CASE 8. The patient was white and 29 years of age. The testis was retained in the abdomen on the left side. On microscopic examination the tunica albuginea was not abnormally thickened, but the basement membrane of the tubules was somewhat thickened. The tubular epithelium was atrophic. The stroma consisted of inflammatory edematous tissue with interstitial cells present. The walls of the blood vessels were also thickened.

In this third decade undescended testes of 6 patients were studied. The youngest patient was 20 and the oldest 29 years of age. In all of the inguinal cases there was some atrophy of the tubules. There was no increase of the interstitial cells. It is conceivable that each of these testes would regenerate an entirely normal germinal epithelium if they had been replaced in the scrotum. The tubules of the abdominally retained testis were not without epithelium, although the epithelium seen was atrophic. However, it might have shown evidence of regeneration in its normal location.

It is interesting to note that two of these testes showed early, low grade cancer, and their removal was highly desirable. It is entirely probable that both of these patients in whom cancer was found would at a later date have shown clinical evidence of cancer of the testis.

Fourth decade. CASE 9. The patient was white, single, and 32 years of age. The testis was at the left external inguinal ring. On microscopic examination the tunica albuginea and basement membrane of the tubules were found to be thickened. There was atrophy of the tubular epithelium with partial fibrosis in some of the areas. The stroma was found to be edematous, and very few interstitial cells were noted.

CASE 10. The patient was white, married, and 35 years of age. The testis was in the left inguinal canal. On microscopic examination there was noted a diffuse increase in the interstitial connective tissue. The basement membrane of the tubules was thickened, and there was some atrophy of the tubular epithelium. The interstitial cells were apparently reduced in number.

CASE 11. The patient was white, married, and 36 years of age. The testis was in the right inguinal canal. On microscopic examination the tunica albuginea and basement membrane of the tubules were found to be thickened. A few of the tubules contained unchanged epithelium, but the majority were atrophied. Interstitial cells were present, but were not increased in number (Fig. 5).

CASE 12. The patient was white, married, and 37 years of age. The testis was at the right external inguinal ring. On microscopic examination the tunica albuginea and basement membrane of the tubules were prominent. Some of the tubules contained a well developed epithelium, whereas others revealed atrophy. Only a few interstitial cells were present (Fig. 6).

CASE 13. The patient was white and 39 years of age. The testis was probably in the inguinal canal. On microscopic examination the tunica albuginea was found to be thickened. There was marked atrophy of the tubules, and in some areas only the tubular outline remained. The cells comprising the tubular epithelium in areas were devoid of cytoplasm and contained only occasional fragmented nuclei, while the lumen of some of the tubules was filled with cellular débris. The walls of the blood vessels were very thick. The interstitial cells were very few in number.

Fig. 5. Photomicrograph in Case 11. The tubules show slight atrophy and a few interstitial cells are seen. ×80.

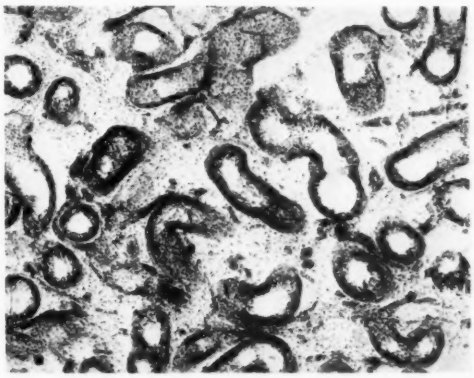

Fig. 6. A few of the tubules show a well developed epithelium, while others reveal atrophy. An occasional interstitial cell is seen. ×47.

In the fourth decade specimens of undescended testes from 5 patients were obtained for study. The germinal epithelium in Cases 10, 11, and 12 did not show severe degenerative changes. There is nothing to indicate that these testes might not have developed a normal epithelium had they been placed in the scrotum. In Case 9 there was some evidence of atrophy, but in some of the tubules the epithelium was in a fair state of preservation. It is possible that this testis would have developed normal epithelium had it been placed in the scrotum. In Case 13 the atrophic changes had progressed to such an extent that it is extremely doubtful that regeneration would have taken place had it been transferred to the scrotum.

Fifth decade. CASE 14. The patient was white, married, and 40 years of age. The testis was at the right external inguinal ring. On microscopic examination the tunica albuginea as well as the basement membrane of the tubules were seen to be thickened. Some tubules were atrophied. There was very marked inflammatory interstitial tissue.

CASE 15. The patient was white, married, and 41 years of age. The testis was in the left inguinal canal. Microscopic examination revealed a thickened tunica albuginea and the basement membrane. Some of the tubules showed beginning atrophy. There was an increase in the fibrous connective tissue of the stroma with areas of hyalinization. A few interstitial cells were seen (Fig. 7).

CASE 16. The patient was white, married, and 45 years of age. The testis was in the right inguinal canal. Microscopic examination revealed hyalinized tubules and no interstitial cells (Fig. 8).

CASE 17. The patient was white, married, and 45 years of age. The testis was retained in the abdomen on the left. Microscopic examination revealed a thickened tunica albuginea. There was marked atrophy of the tubules and in areas hyperplasia of the interstitial cells with brownish pigment. In the intertubular spaces were masses of cells, which, in one pathologist's opinion, consisted of undifferentiated germinal cells but showed no evidence of malignancy. Another pathologist, in examining the section, noted that some of the nucleoli were large (Fig. 9).

Fig. 7. Moderately atrophic tubules adjacent to the tunica albuginea. ×50.

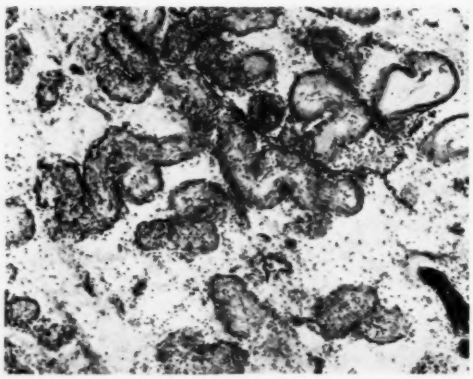

Fig. 8. The tubules are hyalinized. ×35.

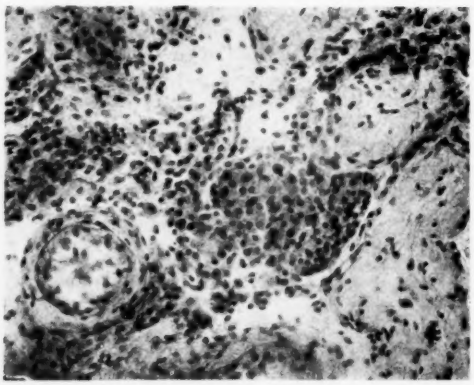

Fig. 9. Interstitial cells in the intertubular spaces which are partially undifferentiated and occasionally contain large nucleoli. ×140.

In Case 14 there was some atrophy and inflammation in the interstitial tissue. In Case 15 there was just beginning atrophy of the tubules. It is possible that the epithelium in Cases 14 and 15 might have developed had the testes been placed within the scrotum; Case 15 was the most promising. In Case 16 the tubules were hyalinized. With hyalinization as seen in Case 16 it would seem very improbable that spermatogenesis could ever occur in this organ. In Case 17 the tubules were markedly atrophied. There were hyperplastic interstitial cells of unknown function and of questionable morphology, which would make its removal justifiable.

Fig. 10. Fibrosis and hyalinization of the tubules. ×40.

Sixth decade. CASE 18. The patient was white, married, and 52 years of age. The testis was in the left inguinal canal. On microscopic examination the testis was found to be composed of fibrous connective tissue and adipose tissue. No remaining tubules were seen.

CASE 19. The patient was white, married, and 52 years of age. The testis was in the right inguinal canal. On microscopic examination the basement membrane of all of the tubules was found to be thickened and there were fibrosis and hyalinization of the majority of the tubules. An occasional interstitial cell was seen (Fig. 10).

The microscopic appearance of the testis in Case 18 was essentially that of fibrous connective tissue with no tubules remaining. In Case 19 the tubules of the testis were largely fibrosed and replaced with hyaline tissue. It seems improbable that either of these testes would ever regenerate a functional germinal epithelium regardless of the position.

Seventh decade. CASE 20. The patient was white, married, and 62 years of age. The testis was at the left external inguinal ring. Microscopic examination revealed that the tubules were atrophied and almost completely hyalinized. No interstitial cells were seen. The stroma was slightly edematous.

CASE 21. The patient was white, married, and 62 years of age. The testis was in the right inguinal canal. On microscopic examination the tubules

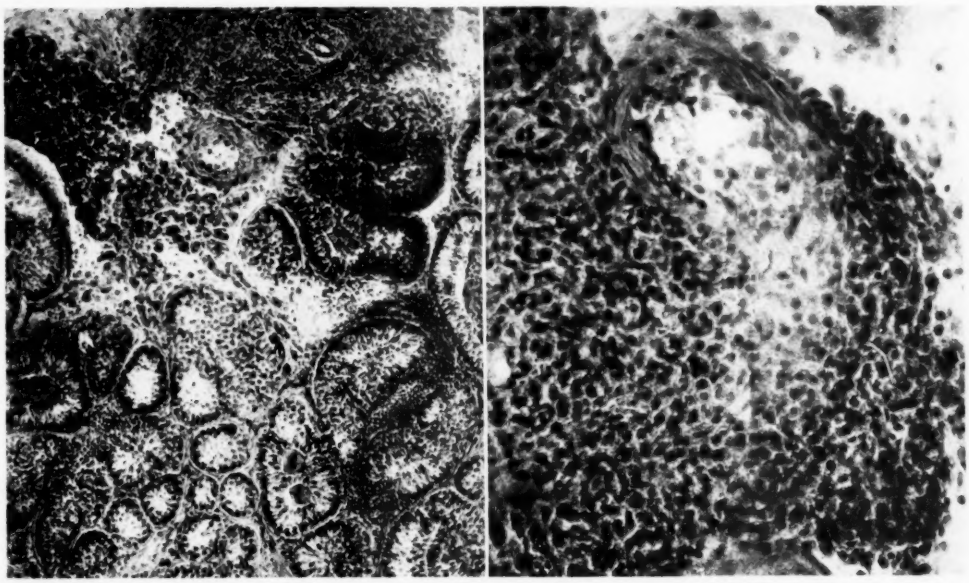

Fig. 11. a, left. Hyperplasia or early cancer of tubules. In the upper portion of the illustration is seen a mass of interstitial cells of questionable morphology. In the upper left hand corner are interstitial cells with larger nucleoli and brown pigment. ×100. b, Higher magnification of a different field of the same specimen. Interstitial cells with large nucleoli which apparently originate in the tubule. ×230.

were found to be replaced with fibrous connective tissue and hyaline. The tubular outlines were recognizable but entirely devoid of any epithelium. No interstitial cells were seen. The stroma contained some inflammatory cells.

CASE 22. The patient was white, married, and 62 years of age. The testis was in the left inguinal canal. On microscopic examination the tubules were seen to be replaced with hyaline. A few interstitial cells remained. There was a chronic interstitial inflammatory reaction.

CASE 23. The patient was white, married, and 65 years of age. The testis was in the left inguinal canal. On microscopic examination the testis was found to be completely replaced with fibrous connective tissue with areas of hyalinization. No tubular outlines remained.

CASE 24. The patient was white, married, and 67 years of age. The testis was retained in the abdomen on the right. Microscopic examination revealed the tunica albuginea, walls of the blood vessels, and the basement membrane of the tubules to be thickened. The interstitial cells were reduced in number in some areas and were seen as hyperplastic masses in other areas (Fig. 11a). In the midportion of the testis, well removed from the surface, was seen what was in the opinion of two pathologists an early adenocarcinoma. Another pathologist, in examining this area, was unwilling to call these cells truly cancerous, but it was undeniable in his opinion that they represented the extreme of hyperplasia. Furthermore, he regarded another group of apparently interstitial cells as being malignant, and he demonstrated one field in which it would seem that the origin of these cells was in the tubules (Fig. 11b).

In Cases 20, 21, 22, and 23 fibrosis and varying degrees of hyalinization of the tubules were noted, and it is inconceivable that these four testes should have regained their normal spermatogenic function had they been placed in the scrotum. In Case 24 is seen what is regarded by two pathologists as adenocarcinoma, grade 1. However, this diagnosis was not in accord with the opinion of the third pathologist, who considered this questionable area of tubules to be hyperplastic. Two pathologists regarded the hyperplastic whorls of interstitial cells as not being malignant, although one of the two went so far as to say that these interstitial cells may be regarded by some as precancerous. The third pathologist was very definite in stating that he regarded these interstitial cells as being malignant, and he demonstrated to our satisfaction that their

origin was tubular. He described the lesion as being a spermatoblastoma.

SUMMARY

This study seems to suggest that there is progressive deterioration as the years go by. Thus in the second decade one specimen showed germinal epithelium which might have developed normally. The other case showed very complete degeneration, and it is not improbable that this was an undeveloped testis from the start. In the third decade all of the 6 specimens showed some degree of atrophy, but all showed remaining epithelium which could have gone on to satisfactory development. In the fourth decade 4 of the 5 specimens showed epithelium which might have developed normally. The fifth specimen showed very extensive atrophy. In the fifth decade 2 of the specimens showed epithelium which might have developed, while the 2 others had gone on to very complete destruction. One of these was a testis retained within the abdomen, in which, on theoretical grounds, one would expect more complete atrophy. In the sixth decade both of the specimens showed very complete fibrosis and destruction. It did not seem reasonable to assume that these could show any important degree of regeneration. In the seventh decade all of the 5 specimens showed extensive degeneration and hyalinization, and were apparently beyond recall. Attention is called to the absence of hyperplasia of the interstitial cells of Leydig except in Figures 9 and 11a.

EVIDENCE OF MALIGNANT DISEASE

It is interesting, and we think important, to note that in the normal routine examination of these 24 specimens, 3 were found which showed evidence of cancer. Two of these were in the third decade and showed a lesion described as adenocarcinoma. The third was in the seventh decade and showed a lesion which was more controversial. Two pathologists regarded the lesion as early adenocarcinoma. With this opinion the other pathologist disagreed, however, regarding the cells as showing abnormal hyperplasia.

These findings seemed to us very importantly to strengthen the opinion that the abnormally placed testis is much more likely to develop cancer than the normally placed testis. It further suggests that rather more careful study of misplaced testes removed at operation or found at autopsy might shed still more light upon this question, which is of great importance.

BIBLIOGRAPHY

1. Moore, C. R. The behavior of the testis in transplantation, experimental cryptorchidism, vasectomy, scrotal insulation, and heat application. Endocrinology, 1924, 8:493–508.
2. Idem. Properties of the gonads as controllers of somatic and psychical characteristics. VI. Testicular reactions in experimental cryptorchidism. Am. J. Anat., 1924, 34:269–316.
3. Moore, C. R., and Oslund, Robert. Experiments on the sheep testis—cryptorchidism, vasectomy and scrotal insulation. Am. J. Physiol., 1924, 67:595–607.
4. Moore, C. R., and Quick, W. J. The scrotum as a temperature regulator for the testes. Am. J. Physiol., 1924, 68:70–79.
5. Wangensteen, O. H. The undescended testis. An experimental and clinical study. Arch. Surg., 1927, 14:663–731.
6. de Winiwarter, H. Histologie du testicule ectopique. Epithélium séminal. Compt. rend. Soc. de biol., 1928, 99:643–644.
7. Idem. Histologie du testicule ectopique. Tissu interstitiel. Phénomènes sécrétoires. Compt. rend. Soc. de biol., 1928, 99:645–647.

PREVENTION OF RECURRENT RENAL CALCULI

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A SURVEY of the literature reveals a paucity of publications devoted to the problem of recurrent renal lithiasis following conservative operative intervention.

That calculi should recur frequently seems obvious when the initiating causes of stone formation are not corrected by the surgical removal of a calculus. Certainly, we are treating the "effect" and not the "cause" of this pathological condition. It is true that a calculus may be removed surgically or a small stone may be expelled spontaneously and that a recurrence may never be experienced; however, a sufficient number of cases of recurrence of stones has been reported to make a consideration of this problem of utmost importance, and it becomes obvious that before permanent relief from calculi may be secured, the underlying causes must be corrected and the factors eliminated which frequently are associated with the production of urinary calculi.

CLASSIFICATION

Herbst classifies recurrent calculi in the following manner:

1. True recurrence or the new formation of a calculus after the complete removal of the original stone (Fig. 1).

2. False recurrence or a persistence of stones or fragments of a calculus which were overlooked at the time of operation (Figs. 2 and 3).

INCIDENCE

It is difficult to estimate the true incidence of recurrent calculi. Unless a roentgenogram is made routinely following operation, a misinterpretation of results will occur, and it becomes impossible later to differentiate between a newly formed calculus and one which was overlooked at the time of operation.

It is true also that minute fragments of a stone or sand may not be demonstrated in a postoperative roentgenogram, although they may serve as nuclei for further stone formation. However, by placing a small film behind the delivered kidney for roentgenographic study as suggested by Quinby or by fluoroscopic examination as described by Braasch and Carman, the presence of small stones or retained fragments frequently may be revealed, and these may be removed before the operation is completed. In a review of the cases of calculi recurring after operation for renal stones since 1917 at the Mayo Clinic, Braasch found that shadows of stones were present in the kidney in roentgenograms made immediately after operation in 31 of 685 cases.

The frequency with which calculi recur following operation varies considerably according to different authors. In 1915, Cabot and Crabtree, in reviewing the results of a series of operations for renal stone in Massachusetts General Hospital, stated that "recurrence" occurred in 56 per cent of patients treated by

Fig. 1 True recurrent bilateral calculi.

Fig. 2. Four calculi in the right kidney. The large calculus was removed at operation (March 2, 1934) but the three small stones were overlooked.

Fig. 3. False recurrent calculi 9 months later (December 14, 1934). Note rapid enlargement of calculi since operation.

nephrotomy and in 51 per cent of those treated by pyelotomy. Brongersma reported the incidence of recurrence to be about 16 per cent in instances in which infection of the kidney was not present or in which only a slight infection was noted. In his series in which severe infection of the kidney was present, recurrence occurred in about 50 per cent of the patients following operation.

Barney in 1922, reviewed the results secured in a series of patients operated upon for renal stones at the Massachusetts General Hospital, and reported recurrence in 32 per cent of the cases. Of this group, however, postoperative roentgenograms were made in 20 cases, and a stone still was present in the kidney in 9, or 45 per cent. Braasch and Foulds in 1924, stated that calculi recurred in 10.79 per cent of patients who were operated upon for renal calculi at the Mayo Clinic, and Herbst noted a recurrence of approximately 15 per cent. In 1927, Hunner (15) reviewed the results secured in his series and stated that recurrence followed 9.5 per cent of operations for renal and 4.4 per cent of operations for ureteral stones. In our series of cases, from 1923 to 1932, a recurrence of 16.4 per cent has been noted. Thus, it is evident that recurrent calculous formation is a complication which cannot be considered lightly, and the empirical measures employed in the past did not prevent recurrence in from 10 to 15 per cent of the cases.

Frequently, the prolonged presence of the calculus in the kidney has produced marked impairment of renal function, a superimposed renal infection, marked hydronephrosis or pyonephrosis which contra-indicates a conservative operation. However, if the kidney on the opposite side is normal when nephrectomy is performed, the development of a calculus in the sound kidney occurs relatively infrequently. In his statistical study, Rovsing found that calculi developed in the sound kidney after removal of the pathological kidney only once following 31 nephrectomies. In our series of cases, stones formed in the opposite kidney in 2.8 per cent of the cases.

The formation of calculi in the opposite kidney, therefore, occurs quite infrequently following nephrectomy—approximately in from 2 to 4 per cent of the cases.

The type and consistency of calculus, i.e., large or small, soft or hard, also influence the percentage of formation of calculi following operation. The larger percentage of recurrence following the removal of soft stones undoubtedly is due to retained sand or fragments and cannot, therefore, be termed true recurrence.

In the cases in . hich the stones extend into the calyces, a higher percentage of recurrences was noted in our cases than when the stone was confined to the pelvis itself. As in this group, incomplete removal of the calculus may occur, or damage to the calyx, infundibulum or renal pelvis may be instrumental in the production of the higher incidence of recurrence. Braasch (5) has stated that recurrence following removal of small stones exceeded that following large ones, 13.48 and 9.66 per cent, respectively. In our cases, if we included in the group of large calculi those which extended into the calyces, the percentage of recurrence, 11.98 per cent, is approximately the same provided the postoperative roentgenogram did not reveal retained calculi.

The operative results in cases of bilateral calculi are not as satisfactory from the viewpoint of recurrence. In the large percentage of cases, bilateral infection is present, and Joly states that the infection usually persists following operation and recurrence is the rule. Brongersma reported 36 cases in which 75 operations were performed, and recurrences developed in 14 instances. Braasch (5) has stated that in most cases, the probable period of time is limited in which stones may form again, and the average interval between operation and recurrence is 2 years. However, in many instances, recurrences will develop at a later period, especially in patients between the ages of 20 and 40 years, and in some instances, small calculi will be passed spontaneously.

FACTORS ASSOCIATED WITH FORMATION OF CALCULI

In the consideration of the prevention of formation of calculi, obviously the factors associated with their formation must be considered.

Infection. Keyser, in reviewing a series of 12 cases of intensive recurrent lithiasis at the Mayo Clinic, noted positive cultures from the bladder in 6 cases, negative culture in 1 case, and in 5 cases, no culture was reported.

Rovsing expressed the opinion that a urea splitting organism, especially the staphylococcus, was most frequently associated with recurrent calculi. Braasch (5), however, states, "Gross evidence of tissue infection did not seem to be a factor favoring recurrence. In fact, the percentage of recurrence was less than average when the areas of renal infection were thoroughly drained and all fragments cleanly removed."

One of the most critically and carefully studied series of cases is that of Bugbee, who reviewed the results of operations for nephrolithiasis. This investigation was made to determine the presence of a pre-existing pyelonephritis as a possible factor in the formation of renal calculi. A definite history of pyelonephritis was elicited in 23 cases, and in 17, treatment had been administered during the initial attack. In the 6 remaining cases, the infection had been treated by other physicians. Although roentgenograms did not demonstrate the presence of a calculus at the time when each patient was first seen, stones subsequently developed in all these patients. The reaction of the urine and the organisms cultured were noted in each case at the time of the original attack and during the subsequent attacks, and finally the composition of the calculi was determined. It is of interest to note that the urine was acid in reaction and that colon bacilli were the offending organisms in 16 cases during the first attack. In 9 of the 16 cases, the urine later became alkaline and staphylococci were the predominating organisms; in 5, the urine remained alkaline through repeated attacks; in 1 case, the urine was neutral in reaction and in another, it varied from faintly acid to neutral. The composition of the calculi formed in the presence of acid urine was calcium oxalate; in alkaline urine, largely phosphatic.

The studies of Rovsing showed that 68.18 per cent of all recurrences occurred in kidneys

which were infected either primarily or secondarily with bacteria decomposing urea. In 15.9 per cent of cases, recurrences developed in sterile urine.

True recurrence is relatively infrequent in aseptic kidneys or in those infected with Bacillus coli alone, but when the urea splitting organisms are present, especially the proteus organisms, calculi develop or recur with considerable rapidity, enlarge rapidly, and eventually destroy the kidney. Rosenow and Meisser also emphasized the part played by bacteria in the production of urinary calculi and its relationship to recurrent formation of calculi. They demonstrated the selective action of the green streptococcus in the formation of calculi.

Hyperparathyroidism. Studies which demonstrate the relationship between the parathyroid glands and the formation of calculi have been reported by Albright and Bloomberg (1), Barney (3), Chute (10), and others. Albright recently reported a series of 23 proved cases of hyperparathyroidism from Massachusetts General Hospital in which X-ray studies revealed renal calculi in 15 patients. Examination of the blood in cases of hyperparathyroidism reveals a high level of serum calcium, a low level of serum phosphorus, and an increase in the elimination of the calcium and phosphorus in the urine. Roentgenograms may reveal the presence of bone disease, but in Albright's series, evidence of bone disease without a coexisting renal disease was present in only 5 patients and he states that the findings in these cases suggest that renal disease is a more frequent manifestation of hyperparathyroidism than is bone disease.

If the calculi in a particular case are associated with hyperparathyroidism, the surgical removal of the calculus from the kidney probably will be followed by recurrence of the stones. Therefore, this condition must be treated before removal of the calculus is performed except in those exceptional cases in which delay in the operation is contraindicated.

Cystinuria. Cystine nephrolithiasis is a more unusual type of calculous formation. Seeger and Kearns stated that since Wollaston's discovery of cystine in 1810 (28), 181 cases of cystinuria have been reported, and it is interesting to note that in 124 of these, calculi have also been present.

Cystinuria is now believed to be due to an error in metabolism which Neuberg classified as follows:

1. The mild type in which there is a tolerance for tyrosin, cystine, and asparaginic acid.
2. The type in which cystine is excreted and there is present also a diminished power to oxidize the other amino-acids on feeding.
3. The type in which the disturbance of the intermediate protein metabolism is so advanced that other amino-acids (tyrosin and leucin) are excreted as well as cystine.

Heredity is an important factor and several authors have reported the occurrence of cystine calculi in more than one member of a family.

The presence of cystine crystals or the presence of cystine in solution in the urine should draw attention to the fact that the calculus may be composed chiefly of cystine. However, this substance may not always be noted in the urine of patients with cystine calculi and its disappearance from the urine at intervals has been observed. In this type of case, restriction of proteins is advisable in conjunction with high vitamin A alkaline-ash diet to prevent recurrence.

Phosphaturia. Increased elimination of oxalates and uric acid in the urine as well as persistent phosphaturia are associated with calculous formation and therefore present an important problem in the prevention of stone formation. This is especially true in the patient with phosphaturia, and while it is also recognized that infection probably is the most frequent cause of persistent phosphaturia, this is not true in all cases.

Laidley states that three types of phosphaturia may occur:

1. Temporary phosphaturia.
2. Permanent non-infected phosphaturia.
3. Permanent infected phosphaturia.

Temporary phosphaturia may be caused by various metabolic factors. Laidley states that a constant finding in temporary phosphaturia is an increase in the total amount of alkali of the body fluids. The urine may become alka-

line temporarily due to the ingestion of various foods, such as oranges, lemons, and other citrous fruits, as Holmes and Coplan have reported. Certain other foods yield an acid rather than an alkaline ash.

Permanent phosphaturia which is not associated with infection may coexist with a disturbance of the function of the large bowel, and in such cases, the usual amount of earthy phosphates may not be excreted. Laidley has found in his cases that there was an absolute and relative increase in earthy phosphates in the urine of permanent non-infected phosphaturia in contrast to the phosphaturia due to infection in which the earthy and alkaline phosphates eliminated in the urine were within normal limits.

Phosphaturia accompanied by infection is due to a deposition of phosphates by the urea splitting organisms which so frequently are associated with recurrent calculi. Thus, the urine of all patients with renal calculi should be cultured and it should be determined whether the organism has the power of splitting urea.

Oxaluria. Neville has stated that an important factor in the production of oxaluria appears to be a disturbance of the calcium-phosphorus ratio which results in an excessive excretion of calcium which, associated with a deficiency in vitamins B and D, comprises but one symptom of general metabolic disorder. According to this writer, when disturbance of the calcium-phosphorus ratio is the immediate cause of oxaluria, this condition may be corrected by the administration of the deficient vitamins. Braithwaite cited the case of a boy in whom hematuria was associated with the passage of typical oxalate crystals in the urine. Under dietary management, the oxalate crystals disappeared from the urine and hematuria no longer occurred. Mitchell likewise cited the case of a student who passed enormous amounts of oxalate crystals in the urine and these disappeared after dietary management. The oxalate radical is derived mainly from the food, but occasionally oxalic acid may be formed in the intestines from excessive fermentation.

Uric acid. Normally, from 0.3 to 1.2 grams of uric acid are excreted daily, this amount, however, depending largely upon the diet. In the presence of lithiasis, tiny crystals of uric acid or urates which are derived from exogenous or endogenous sources or both may be noted in the voided urine. The exogenous source of uric acid is from the food, and especially from the purine bodies which are derived from the nucleo-albumin which is present in large amounts in kidneys, pancreas, and liver. The endogenous uric acid is derived from substances which result from the breakdown of cellular tissues.

Vitamin A deficiency. In a series of 16 cases of nephrolithiasis which we have studied recently, we have found a positive Jean's test (a test for vitamin A deficiency) in 11. In 2 additional cases, carotene in oil capsules had been prescribed 2 months previous to our examination so the test gave normal findings. In one case in which hyperparathyroidism was associated with bilateral renal calculi, a positive test for vitamin A deficiency was found. Similar results are being noted in other cases of renal calculi, but as yet the test has not been performed upon a sufficient number of patients to warrant definite conclusions. In view of the experimental work reported previously on the production of urinary calculi by a diet deficient in vitamin A (12) and their solution by restoration of vitamin A to the diet, we believe that a Jean's test should be made in all cases of renal calculi.

Vitamin A is prescribed not only to overcome the vitamin deficiency present, but also because of its specific effect upon the epithelial cells. In some instances, loss of the epithelium of the renal pelvis is so complete that ulceration has occurred which is due to the constant trauma of the tissue by the calculus. On several occasions, at the time of removal of a calculus from the kidney, I have removed for study a small piece of the kidney pelvis contiguous to the calculus. In 3 instances the ulcerated area was covered with phosphates and minute calculi and sand. The fibrin coming from the ulcerated area formed a network to which the phosphates adhered and enlargement occurred by further deposition of phosphates at this site. Thus, in the presence of phosphaturia, the sediment and crystals may adhere at the point of ulceration, and fibrin

binds the particles together. This small accumulation of phosphates may then be expelled spontaneously or it may drop into the dependent lower calyx and enlarge by further deposition on the minute calculus. In the presence of urea splitting organisms, the calculus enlarges rapidly. Similarly, in the presence of uric acid crystals or urates in the urine, oxaluria or cystinuria, the respective crystals or sediment may adhere to a local lesion in the kidney whether it be due to trauma, vitamin A deficiency, or infection and thus be instrumental in the production of calculi having these chemical constituents. No medication is comparable to vitamin A in its healing effect postoperatively on the epithelium of the kidney pelves and it should, therefore, be prescribed routinely.

From a consideration of these factors which are of importance in the formation of calculi, and with the knowledge that most of them may be controlled by dietary measures, it is apparent that dietary supervision following operation is of inestimable value in the prevention of the recurrence of stones. It is imperative that crystals and sediment of oxalates, uric acid, cystine, and phosphates be eliminated from the urine.

In the experimental laboratory, we are now able to produce stones composed first, of calcium and magnesium phosphate, second, of calcium carbonate, and finally, of uric acid. *The composition of the calculi varies with the reaction of the urine, the sediment and the type of crystals present.* This finding again emphasizes the necessity for the postoperative elimination of the cause of any crystal formation in the urine by the use of proper diet and medication.

PRE-OPERATIVE INVESTIGATION

A most thorough examination is essential in all cases whether renal calculi be primary or secondary. I have employed the following routine for the past 3 years: A careful history regarding the diet is essential to the discovery of any gross deficiency in the diet of the patient. Moderate degrees of deficiency in vitamin A cannot be determined from the history alone, and in this regard, it is important to remember that the vitamin A content of dairy products varies considerably with the season of the year. An interesting study in this regard was that of the Ohio Experimental Station in which they found that when cows are on winter feeding, some milk contains less than half as much vitamin A as when the cows are on summer feeding in pasture. Thus, one of the chief sources of vitamin A which is contained in milk, butter and cream, is altered considerably during the winter months. Likewise, eggs, toward the end of the laying season, frequently contain only half the vitamin A content that they do in the earlier part of the year.

A familial history of calculi may be elicited as has been noted in cases of cystine lithiasis. A thorough physical examination should be made which includes a careful examination of the neck to discover the presence of a parathyroid tumor.

A plain roentgenogram is taken to determine the presence of a calculus in the kidney, to ascertain whether bilateral calculi are present and whether coexisting stones are present in the ureters or bladder. This is followed by a cystoscopic examination. After examination of the bladder, catheters are passed to both kidney pelves and specimens of urine from each are collected for routine examination, for determination of the hydrogen-ion concentration, culture, stained smear of the sediment, and examination of the type of crystals which may be present. This is followed by a fractional phenosulphonphthalein test. Pyelograms may be made at this time.

The following day, after the spasm of the ureters due to the passing of ureteral catheters has subsided, an intravenous urogram is done. From the urogram, further evidence of renal function is secured, and it may be determined whether or not the calculus is producing an obstruction to the passage of urine from the kidney. This also will reveal in most instances whether stasis due to stricture of the ureter is present. The urogram is of the utmost value in determining whether the patient should be treated conservatively by dietary measures or whether surgical intervention is required. Routinely, blood sugar, urea, creatinin, calcium, phosphorus, uric acid, and phosphatase determinations are secured. It is

extremely important that a hydrogen-ion concentration determination be made of the urine from each kidney. Frequently, the hydrogen-ion concentration of the bladder urine is not an accurate index of the hydrogen-ion concentration of the urine from each kidney. I have seen several cases in which the hydrogen-ion concentration of the urine from a kidney which contained a calculus—especially of the phosphatic type or when an infection due to the urea-splitting organism was present—had an alkaline reaction with a hydrogen-ion concentration of 7.8 or 8, while on the opposite, normal side, the hydrogen-ion concentration was from 4.6 to 4.8. Since a normal kidney has better function and is eliminating more urine than the pathological kidney, the reaction of the urine in the bladder may be acid and may have a hydrogen-ion concentration value of from 5 to 5.4. Thus, an erroneous conclusion may be drawn regarding the true reaction of the urine from the kidney which contains the stone (Table I).

TABLE I.—BEFORE OPERATION

Catheterized ureters
Microscopic Examination

	Left	Right
Turbidity	+	o
Gross blood	++	+
Red blood cells	++	++
Pus	+++	o
Epithelium	o	o
Casts	o	o
Crystals—triple phosphate	+	o
Hydrogen-ion concentration	7.2	5.6
Other organisms—cocci	....	o

Pre-operative investigation of hydrogen-ion concentration of urine from each kidney in a patient with left renal calculus (calcium magnesium phosphate). Note difference in hydrogen-ion concentration of urine from the left kidney containing the calculi (7.2), the normal right kidney (5.6), and the bladder (6.1).

A study of the stained smear is required because in the culture, the cocci may be overgrown by a coexisting colon bacillus infection, while in the stained smear, the staphylococci are discernible. In suspected cases of hyperparathyroidism, the urine should also be studied for an increased elimination of calcium and phosphorus. Complete blood chemistry studies are essential.

If an elevation of the serum calcium and a lowering of the serum phosphorus be present, further studies are necessary to rule out the presence of hyperparathyroidism and roentgen studies of the bones are most important. Likewise, if there is an elevation of the blood uric acid, the purines in the diet must be minimized.

Finally, if a small stone has been passed spontaneously or if one which has been removed surgically is available, it is examined to determine the chemical constituents.

OPERATION

Pelviolithotomy. There is a marked tendency toward conservatism in renal surgery. Pelviolithotomy is the procedure of choice in the removal of calculi from the renal pelvis or of small stones from the calyces which are not associated with a narrowing or stricture of the infundibulum. Stones which apparently are too large to be removed from the pelvis by pelviolithotomy without considerable trauma at times may easily be removed by the method described by Zuckerkandl in 1908 for inferior pelviolithotomy or by pyélotomie élargie which Marion described.

In more than 80 per cent of the conservative operations for the removal of renal calculi, pelviolithotomy has been the procedure of choice in our cases. The incision in the pelvis should be sutured with No. 00 plain catgut, care being taken that the suture passes through only the serosal layer of the pelvis and not through the mucosa into the kidney pelvis itself. In this way the suture cannot act as a foreign body and form a nucleus for the formation of a recurrent calculus. There is no doubt but that the simplicity of this surgical operation with its assurance of a minimum of trauma accounts for the lower incidence of recurrent formation of calculi following this operation.

Nephrolithotomy is employed in cases in which the calculus cannot be removed without trauma by the simpler method of pelviolithotomy. When a calculus is confined to the calyx and when the infundibulum is too narrow to permit its extraction through the pelvis with a stone extractor, a localized nephrolithotomy may be performed. Frequently, the small stone which is retained in a calyx may obstruct its outlet and considerable dilatation of the calyx may occur with a thinning out of

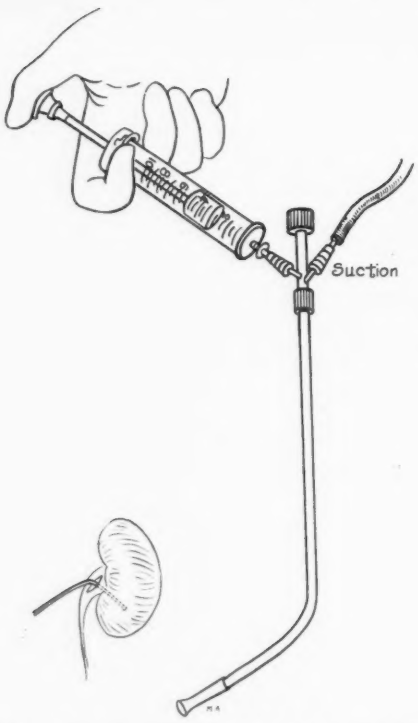

Fig. 4. Suction apparatus. Used for irrigating calyces of kidney and for removing small stones.

the renal parenchyma over the calyx. Then a small incision over the dilated calyx suffices for removal of the stone. In the presence of marked infection and stasis in such a dilated calyx, a heminephrectomy may be employed with excellent end-results.

In the presence of larger staghorn stones, a more extensive nephrolithotomy may be necessary. The bleeding can easily be controlled by compression of the vessels of the pedicle. In such cases, a tube should be left in to facilitate drainage and for treatment in cases of infection. However, nephrolithotomy should always be performed as conservatively as possible.

Nephropelviolithotomy may be employed in some cases in which technical difficulties arise; however, in the majority of cases calculi can be removed by pelviolithotomy or nephrolithotomy.

Nephrectomy. In certain cases, of course, conservative treatment cannot be employed. In the presence of marked infection (calculous pyonephrosis), considerable impairment of renal function, or cases in which the calculi are associated with coexisting pathology, such as renal tuberculosis or tumor, nephrectomy is necessary.

Following the removal of a calculus from the kidney, the suction apparatus which was devised by Dr. Lower is used in all cases (Fig. 4). The rubber tipped tube is passed into the kidney pelvis and then into each of the calyces. By means of a two-way valve, the calyx may be irrigated with saline solution and suction then is applied. Frequently, we have found small fragments of stone and sand adherent to the rubber tip which easily might have been overlooked if this instrument had not been used. We have found it to be of inestimable value in thoroughly cleansing the calyces and kidney pelvis following the extraction of a stone.

POSTOPERATIVE MANAGEMENT

A roentgenogram is secured after operation in all cases before the patient is discharged from the hospital. If a faint shadow is seen in one of the calyces, lavage of the kidney pelvis with a 1 per cent solution of phosphoric acid is employed as Randall has advised. Regardless of whether a shadow may be demonstrated, I usually lavage the renal pelvis in this manner at the time of postoperative cystoscopy or when ureteral dilatation is performed, if it is deemed advisable for the particular case.

ELIMINATION OF STASIS

Urostasis seems definitely to be associated with recurrent formation of calculi. Hunner (14) has demonstrated this relationship and well illustrated the excellent results that may be secured by its elimination. When small stones have been passed spontaneously or when cystoscopic manipulation has facilitated their expulsion, trauma may have produced a stricture with resultant stasis of the upper urinary tract. Dilatation of the ureter should be employed following operation to overcome such a condition.

ERADICATION OF INFECTION

The infections which are associated with the recurrent formation of calculi may be classified in the following two groups:

1. Infection confined to the genito-urinary tract.

2. More distant foci of infection are found in the teeth, tonsils, cervix, prostate, and colon.

In view of the excellent observations and experimental work of Rosenow and Meisser, foci of infection should be eliminated routinely following operation. Of prime importance is the eradication of infection in the kidneys. A careful determination of the organism which is producing the infection is essential. In the absence of stasis or when a mild renal infection is present, ammonium chloride and methenamine usually will suffice; however, there should be no hesitancy in resorting to the ketogenic diet if these measures fail.

In the presence of the colon bacillus infection or of staphylococci, good results usually may be secured by urinary antisepsis or the ketogenic diet. In my experience, the proteus infection is extremely difficult to eradicate. During the past 6 months, I have seen 9 cases of recurrent bilateral nephrolithiasis with bilateral proteus infection. All these patients had been treated excellently elsewhere by ketogenic management without any benefit; in fact, the hydrogen-ion concentration of the urine could not be changed to the acid side. Similar results occurred under my care; however, after the high vitamin A acid-ash diet was followed for from 3 to 4 months, the infection was eradicated in 4 of the 9 cases. In the 5 remaining cases, the proteus infection still is present.

CORRECTION OF VITAMIN A DEFICIENCY

As stated previously, the Jean's test recently has revealed the presence of vitamin A deficiency in 11 of 16 patients who had renal calculi. Due to its specific effect on epithelial structures, vitamin A should be prescribed routinely and if a deficiency is present, this should never be neglected after operation. We usually prescribe one carotene in oil capsule three times daily for a period of 1 month and then 1 capsule each morning. At the end of 1 month or 6 weeks, a Jean's test is made again to determine whether adequate amounts of vitamin A are being secured. Likewise, in cases of oxaluria, vitamins B and D should be added to the diet since Neville has demonstrated the relationship between oxaluria and a deficiency in vitamins B and D.

CORRECTION OF METABOLIC DISORDERS

As stated previously, if the calculi are due to hyperparathyroidism, this condition must be corrected. If a parathyroid tumor is present, it must be removed or recurrent calculi certainly will develop. Likewise, other metabolic disorders in which cystinuria, oxaluria, or the presence of uric acid crystals and urates are found in the urine, must be corrected to avoid recurrent lithiasis.

DIETARY MANAGEMENT

Experimental evidence led us to believe that the recurrence of calculi could be minimized by adherence to a properly planned dietary regimen and the addition of vitamin A in cases in which surgery had been employed, and we have followed this plan in the past 4 years. Although in many instances, the hydrogen-ion concentration of the urine serves as an index for the planning of accurate dietary treatment, if the patient has been receiving acid or alkaline urinary antiseptics, the hydrogen-ion concentration of the urine will be altered. A careful determination of the chemical constituents of the calculus and the type of crystals and sediment present in the urine is of additional value. As I stated previously, the exact hydrogen-ion concentration of the urine from the kidney which harbored the calculus must be determined in order that a correct dietary regimen may be instituted.

In cases in which the calculus is composed of calcium and magnesium phosphates, carbonate or oxalates, the high vitamin A acid-ash diet is employed routinely. Calculi composed of the calcium, magnesium phosphate, and carbonate form in alkaline urine, and calcium oxalate may be precipitated in quite a wide range of urinary reactions. In these cases, the acid-ash diet shifts the reaction of the urine strongly to the acid side. The basic

TABLE II.—AFTER OPERATION AND DIETARY MANAGEMENT

Catheterized ureters
Microscopic Examination

	Left	Right
Turbidity	o	o
Gross blood	+	+
Red blood cells	++	+
Pus	++	o
Epithelium	o	o
Casts	o	o
Crystals—uric acid	+	+
Hydrogen-ion concentration	4.4	4.6
Other organisms	....	....

After postoperative dietary management, the hydrogen-ion concentration of this patient's (same as Table I) urine shifted too strongly to the acid side (4.4 and 4.6) as indicated by the presence of uric acid crystals.

TABLE III.—AFTER FURTHER ADJUSTMENT OF DIET

Catheterized ureters
Microscopic Examination

	Left	Right
Turbidity	o	o
Gross blood	+	+
Red blood cells	++	++
Pus	++	o
Epithelium	o	o
Casts	o	o
Crystals	o	o
Hydrogen-ion concentration	5.2	5.2
Other organisms	....	....

By further adjustment of the diet, the hydrogen-ion concentration of the urine was maintained at a satisfactory level for this patient (5.2). Note absence of crystals.

diet has an excess acid-ash of 17.3 cubic centimeters which is varied daily according to the hydrogen-ion concentration of the urine. As a general rule, an excess acid-ash of from 20 to 30 cubic centimeters is necessary to maintain the hydrogen-ion concentration of the urine at a point from 5 to 5.2. In some instances, additional oral medication is required to maintain this level. We have found that 7.5 grains of ammonium chloride in enteric coated pills is the most efficacious drug for this purpose and causes less gastro-intestinal symptoms than other acidifying agents. As a diabetic diet must be varied or as the amount of insulin to be administered is determined by the blood sugar studies on the diabetic patient, so is the excess acid-ash in the diet or the medication by mouth accurately determined by the hydrogen-ion concentration of the urine in patients on this routine.

Likewise, when a calculus is formed in alkaline urine and when the postoperative reaction is shifted to the acid side, careful check of the urine for uric acid and oxalate crystals or urates is necessary to prevent the recurrence of calculi. This can easily be accomplished by altering the diet so that the hydrogen-ion concentration of the urine is changed to the point at which urates and uric acid and oxalate crystals do not appear in the urine (Tables II and III).

While in the hospital, the patient is taught to make his own hydrogen-ion concentration determinations of the urine with an instrument which is simple, accurate, and reasonable in price. These determinations are checked with those from our laboratory to insure the accuracy of the technique of the patient. The hydrogen-ion concentration determinations are made half an hour before lunch to avoid the effects of the alkaline tide or of awakening respiration changes.

When the patient leaves the hospital, he is instructed to present his hydrogen-ion determination reports regularly to his family physician who then can maintain the hydrogen-ion concentration of the urine at the desired level by further adjustment of the diet or by altering the medication. An occasional recheck of the hydrogen-ion concentration of the urine from the kidney which originally harbored the calculus also is advisable.

In our experience, recurrent calculi most frequently are composed of calcium and magnesium phosphates, and many also contain carbonates. Such calculi develop in an alkaline urine, and their recurrence can be minimized by the use of the high vitamin A acid ash diet which shifts the reaction of the urine strongly to the acid side. Other therapeutic procedures which have been used in the past are employed also.

Less frequently do we see cases in which the calculi are composed of cystine or urates and which are formed in acid urine. In such cases, the high vitamin A alkaline ash diet is used, the basic diet of which has an excess alkaline ash of 17.3 cubic centimeters. This diet is varied daily until the hydrogen-ion concentration of the urine is shifted to the alkaline side.

Immediately following the operative removal of a calculus which has formed in acid urine, the hydrogen-ion concentration should not be shifted so strongly to the alkaline side that phosphaturia is present or crystals of the various phosphates occur in the urine as recurrent phosphatic calculi may develop. I prefer to maintain the hydrogen-ion concentration slightly on the alkaline side of neutral for a period of 1 month, testing the urine frequently for phosphates and carbonates and examining the urine for crystals. After this period when the vitamin A deficiency has been corrected, the incision in the pelvis of the kidney has healed well and the lesions in the pelvic mucosa have healed by vitamin A therapy, more intense alkalinization may be employed to prevent the formation of a recurrent calculus which has the same chemical constituents as the original stone. As a general rule, a hydrogen-ion concentration of 7.0 to 7.1 is satisfactory if the stone is composed of uric acid but more intense alkalinization may be necessary in cases of cystine calculi. In cases of uric acid calculi, the purines in the diet are restricted also.

While the patient is in the hospital, the dietitian instructs him daily concerning the diet, explaining why certain foods are allowed and others restricted. *The mere listing and prescribing of acid or alkaline ash foods does not suffice—a careful, scientific approach is necessary to determine the percentage of acid or alkaline ash in the diet which is required to maintain the proper hydrogen-ion concentration level in each individual case.*

By careful control of the hydrogen-ion concentration of the urine in addition to the other usual therapeutic procedures, we believe the incidence of recurrent calculi can be reduced to a minimum. However, the closest co-operation between the patient and physician is required.

END-RESULTS

Since we have prescribed the use of a regulated diet high in vitamin A following the operative removal of renal calculi, in addition to the other therapeutic measures usually employed, we have reduced the incidence of recurrences during the past 4 years from 16.4 per cent to 4.7 per cent in our cases. Operation has been performed for recurrent calculi in this series in 2 cases. However, 1 case was a false recurrence and in the second, the patient did not adhere to the regimen prescribed for him. We also have a series of 31 cases in which small calculi were passed at frequent intervals, and all of these patients have been free from symptoms more than 2 years.

In many cases, we have noted an eradication of the infection after the patient has been on the high vitamin A acid or alkaline ash diet for a period of from 2 to 3 months. This is probably due to the maintenance of the hydrogen-ion concentration of the urine at a point unsuitable for growth of the causative organisms.

CONCLUSIONS

1. Recurrent calculus formation occurs with sufficient frequency to be a serious complicating factor in the surgery of nephrolithiasis.

2. Empirical treatment which has been employed in the past does not reduce the percentage of recurrence below 10 or 15 per cent.

3. The high vitamin A alkaline or acid ash diet should be prescribed following operation, the constituents of which depend upon the hydrogen-ion concentration of the urine and the chemical constituents of the calculus.

4. A group of 31 patients who previously experienced frequent attacks of renal colic at frequent intervals and expelled small stones spontaneously, have been free from symptoms more than 2 years by dietary management.

5. During the past 4 years, since this diet has been used in conjunction with other therapeutic agents, recurrence has occurred in 4.7 per cent of the cases. This percentage, which is higher than was anticipated, is believed to be due to the fact that all patients were not given roentgen examinations routinely after operation; thus, some of the recurrences may have been false in type.

REFERENCES

1. ALBRIGHT, F., and BLOOMBERG, E. Hyperparathyroidism and renal disease with a note as to the formation of calcium casts in this disease. Tr. Am Ass. Genito-Urin. Surg., 1934, 27: 195–202.

2. BARNEY, J. D. Recurrent renal calculi. Surg., Gynec. & Obst., 1922, 35: 743–748.
3. BARNEY, J. D., and MINTZ, E. R. Some newer conceptions of urinary stone formation. J. Am. M. Ass., 1934, 103: 741–743.
4. BRAASCH, W. F., and CARMAN, R. D. Renal fluoroscopy at operating table. Radiology, 1924, 2: 222–226.
5. BRAASCH, W. F., and FOULDS, F. S. Postoperative results of nephrolithiasis. J. Urol., 1924, 11: 525–537.
6. BRAITHWAITE, J. V. C. Significance of oxaluria. Brit. M. J., 1930, 1: 15–16.
7. BRONGERSMA, H. Cited by Joly, J. S. Stone and Calculous Diseases of the Urinary Organs, pp. 257–264. St. Louis: C. V. Mosby Co., 1931.
8. BUGBEE, HENRY G. Recurring pyelonephritis as an etiological factor in nephrolithiasis. Tr. Am. Ass. Genito-Urin. Surg., 1932, 25: 121–131.
9. CABOT, H., and CRABTREE, E. G. Frequency of recurrence of stone in the kidney after operation. Surg., Gynec. & Obst., 1915, 21: 223–225.
10. CHUTE, RICHARD. The vital importance of the relation of hyperparathyroidism to the formation of certain urinary calculi and its remedy. New England J. Med., 1934, 210: 1251–1253.
11. HERBST, R. H. Recurrent renal calculus; its cause and prevention. Am. J. Surg., 1931, 12: 58–62.
12. HIGGINS, C. C. The experimental production of urinary calculi in rats. Urol. & Cutan. Rev., 1934, 38: 33–39.
13. HOLMES, R. J., and COPLAN, M. M. A study of the geographic incidence of urolithiasis with consideration of etiological factors. J. Urol., 1930, 23: 477–489.
14. HUNNER, GUY L. Ureteral stricture; report of unusual case, illustrating influence of formation of urinary calculi and on recurring calculi. J. Am. M. Ass., 1924, 82: 509–516.
15. Idem. Calculus of the urinary tract treated by new methods. Tr. South. Surg. Ass., 1927, 40: 1–17.
16. JOLY, J. S. Bilateral urinary calculi. Proc. Roy. Soc. Med., 1933, 26: 923–936.
17. KEYSER, L. D. Relationship of urinary infections to recurrent calculi. J. Urol., 1934, 31: 219–238.
18. LAIDLEY, J. W. S. Phosphaturia. Med. J. Australia, 1930, 1: 306–325.
19. MARION, G. La pyélotomie élargie. J. d'urol., 1922, 13: 1–8.
20. MITCHELL, CLIFFORD. Oxaluria. Clin. Med. & Surg., 1930, 37: 292–293.
21. NEUBERG, C., and MAYER, P. Ueber Cystein. Ztschr. f. physiol. Chem., 1905, 44: 472–497.
22. NEVILLE, D. W. Constitutional factor in oxaluria. Urol. & Cutan. Rev., 1935, 39: 32–33.
23. QUINBY, W. C. Localization of renal calculi by aid of X-ray films made during operations. J. Urol., 1925, 13: 59–60.
24. RANDALL, ALEXANDER. Prevention of recurrence of urinary calculi. Am. J. Surg., 1932, 18: 482–493.
25. ROSENOW, E. C., and MEISSER, J. G. Nephritis and urinary calculi following the experimental production of chronic foci of infection. Collected Papers, Mayo Clin., 1921, 13: 253–256.
26. ROVSING, C. Cited by Fowler, H. A. Coccus infection of the kidney: its rôle in the formation and recurrence of stone. Urol. & Cutan. Rev., 1934, 38: 594–605.
27. SEEGAR, S. J., and KEARNS, W. M. Cystinuric lithiasis. J. Am. M. Ass., 1925, 85: 4–7.
28. WOLLASTON, W. H. On cystin oxide; a new species of urinary calculus. Phil. Tr., 1910, p. 223–230.
29. ZUCKERKANDL, O. Ueber Nierensteine. Arch. f. klin. Chir., 1908, 87: 481–489.

A STUDY OF NEO-SYNEPHRIN HYDROCHLORIDE IN THE TREATMENT OF ACUTE SHOCK FROM TRAUMA OR HEMORRHAGE

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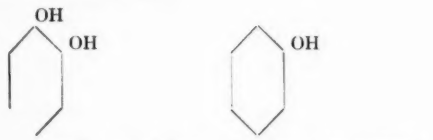
NEO-SYNEPHRIN hydrochloride is a synthetic drug very closely related to epinephrine and has the following structural formula:



Neo-synephrin hydrochloride is used extensively in medicine as a vasoconstrictor, but it also has pronounced systemic effects as pointed out by Kuschinsky and Oberdisse in Germany and by Tainter and Stockton in this country. According to these authors the increased blood pressure following the drug is due to a peripheral vasoconstriction and an increased cardiac output. This has been confirmed by the author for the subcutaneous injection of the drug[1] and Figures 1 and 2 illustrate the results of typical experiments on dogs. The drug may be repeatedly administered without an appreciable decrease in its hemodynamic effects occurring. This is illustrated in Figure 3, which represents the results of a typical experiment. The increased blood pressure following the intravenous injection of a therapeutic dose lasts about 15 minutes, that following a subcutaneous or intramuscular injection from 1 to 2 hours (Fig. 4).

One of the striking differences between neo-synephrin hydrochloride and either epinephrine or ephedrin is that neo-synephrin hydrochloride slows the heart rate and has no tendency to produce irregular rhythms while epinephrine and ephedrin both increase the heart rate and have a tendency to produce irregular rhythms. In addition, knee jerk experiments of the dog by the method of Johnson (2) did not show any stimulation of the spinal cord from ordinary doses, and patients receiving therapeutic doses did not show nervous symptoms as many do with epinephrine or ephedrin.

The drug was given to a number of patients with cardiac disease and the characteristic elevation of blood pressure and the slowing of the heart occurred in all but one (Table I). This patient had frequent attacks of paroxysmal tachycardia and occasional attacks of ventricular tachycardia and was made worse by the drug. Electrocardiograms were taken during the course of all of these experiments and showed no significant changes except the slowing of the heart rate.

In acute traumatic shock or shock from hemorrhage, the striking features are the lowered blood pressure, the weak, rapid, and thready pulse, the marked diaphoresis, and the prostration of the patient who may or may not be in coma.

There are many theories concerning the mechanism of traumatic shock, but in general it is conceded that there is a disturbance of the effective blood volume. Some think that the blood volume is actually decreased as a result of a passage of fluids of the blood into the tissue spaces while others think that the blood passes into the depots of the body as a result of vasodilatation. This subject has been reviewed recently by Frazier.

In general, therapy is usually directed toward restoring the blood volume, conserving body heat, the exhibition of supportive measures, and the elevation of blood pressure by means of the various hemodynamic drugs.

The drugs most commonly used for elevation of the blood pressure are epinephrine and ephedrin, and neo-synephrin hydrochloride.

Epinephrine has certain disadvantages. When given intravenously the effect on the blood pressure is very transitory and its action on the irritability of the heart is very

[1] From the intravenous injection of the drug, the stroke output may be decreased during the sudden and rapid rise of blood pressure, presumably as a result of the marked increased peripheral resistance.

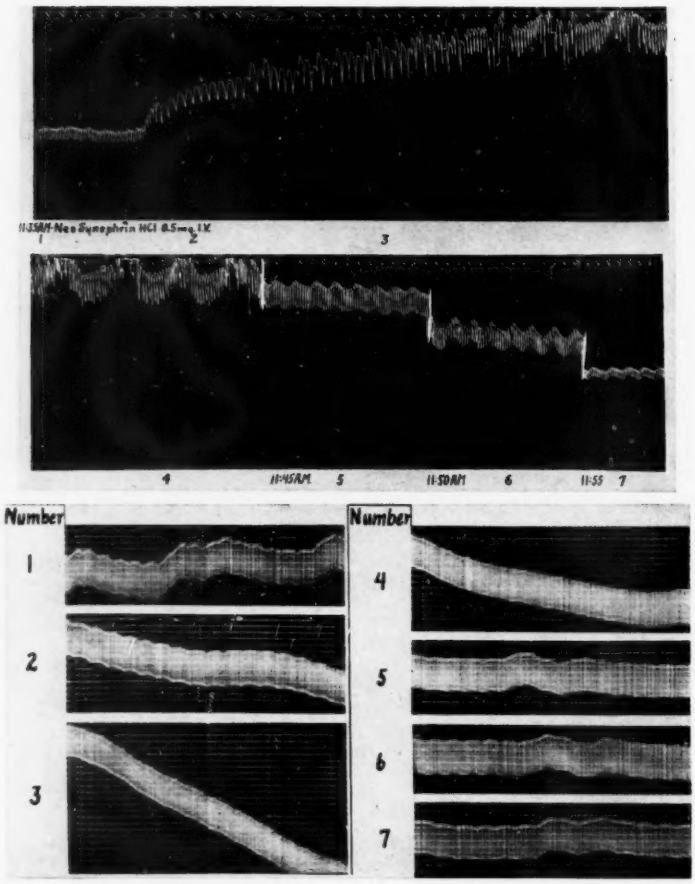


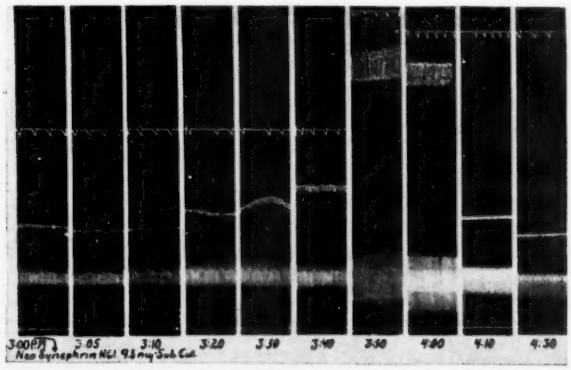
Fig. 1. The effect upon the blood pressure and peripheral circulation of an intravenous injection of neo-synephrin hydrochloride (0.1 mgm. per kilogram) in a 5 kilogram dog. The upper record shows the blood pressure and the lower the leg volume changes. The results are interpreted as a peripheral vasoconstriction from the neo-synephrin hydrochloride. (The method is described by Johnson in Surg., Gynec. & Obst., 1932, 55: 731).

pronounced as evidenced by the occurrence of ectopic beats; even ventricular fibrillation may result. When given subcutaneously, only a slight or no elevation of blood pressure results. In addition to the effects it has on the cardiovascular system, it has a tendency to make some patients very nervous and apprehensive.

Ephedrin has been used with considerable success in the treatment of shock. Johnson (3) reported a series of 10 patients in shock and in whom this drug was advantageously employed, and pointed out that its action on the central nervous system may be as important as the hemodynamic actions of the drug. However, ephedrin has, like epinephrine, a tendency to produce ectopic beats, and in certain cardiac patients may produce very unfavorable reactions.

It was thought that neo-synephrin, on the basis of the pharmacological studies outlined in the first part of this paper, would have the advantages of ephedrin without its disadvantages in the treatment of shock. Accord-

A.



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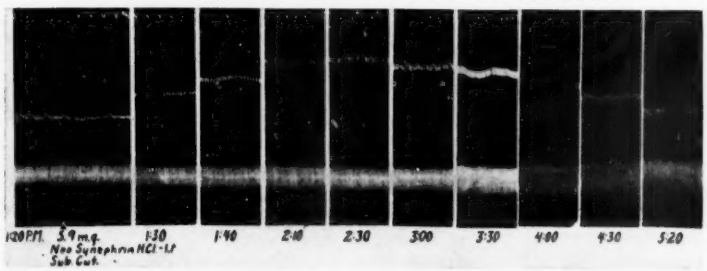

Fig. 2A. The chart and table shows the effects of a subcutaneous injection of neo-synephrin hydrochloride in a 9.3 kilogram dog (1.0 milligram per kilogram) anesthetized with sodium barbital (.25 gram per kilogram intraperitoneally). Note the marked increase in minute and stroke output of the heart associated with the rise in blood pressure.

Time	3:00	3:05	3:10	3:20	3:30	3:40	3:50	4:00	4:10	4:30
Blood pressure	100	97	96	110	122	132	254	244	132	90
Heart rate	102	102	102	108	114	114	84	114	132	132
Stroke output*	1.4	1.8	2.0	2.2	2.8	2.8	2.4	5.4	2.8	2.4
Minute output*	142	182	204	238	320	320	404	608	280	254

*The stroke and minute output are given in cubic centimeters.

Fig. 2B. The graph and table shows the effects of a subcutaneous injection of neo-synephrin hydrochloride (1.0 milligram per kilogram) in a 5.9 kilogram dog anesthetized with sodium barbital (.25 gram per kilogram intraperitoneally). The results on blood pressure, heart rate, stroke, and minute output are given. The stroke and minute output did not change much in spite of the marked increase in blood pressure. This suggests that in this experiment the action of the drug was chiefly on the peripheral vascular system.

Time	1:20	1:30	1:40	2:10	2:30	3:00	3:30	4:00	4:30	5:20
Blood pressure	100	120	138	152	158	148	146	134	118	108
Heart rate	144	144	144	126	120	108	108	90	90	84
Stroke output*	1.8	2.0	2.0	2.2	2.0	2.2	2.6	2.8	3.0	3.2
Minute output*	260	288	288	278	240	238	280	252	270	268

*The stroke and minute output are given in cubic centimeters.

ingly it has been employed in the treatment of 6 patients in the state of traumatic shock with results best demonstrated by the presentation of case reports.

CASE REPORTS

In the following case reports the patients received the usual treatments for traumatic shock, such as fluids, conservation of body heat, etc. These procedures are not recorded as they are more or less routinely employed in the treatment of shock. Neo-synephrin hydrochloride was considered to be only an adjunct to these measures and only the data pertaining to the effect of the drug on the blood pressure and its effect on the pulse have been selected for inclusion in this report of our study.

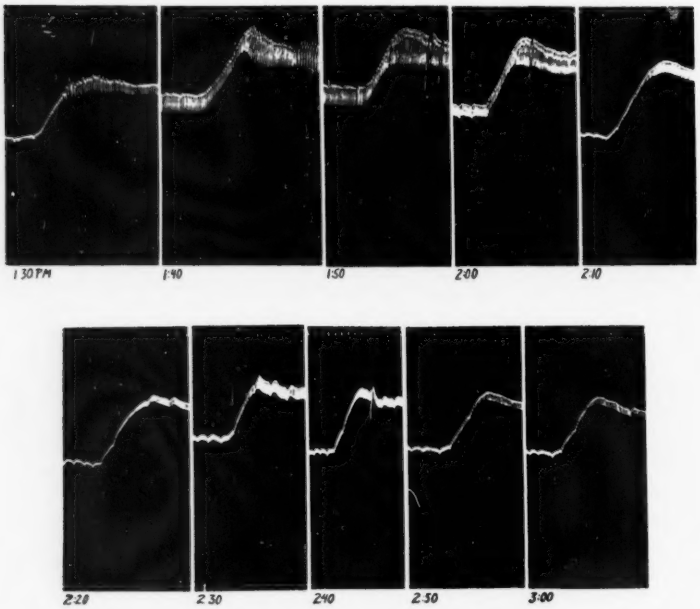

Fig. 3. The effect of repeated doses of neo-synephrin hydrochloride intravenously in a 9.6 kilogram dog anesthetized with sodium barbital (.25 gram per kilogram intraperitoneally). The upper graph shows the carotid blood pressures. An intravenous injection of 0.43 milligram of neo-synephrin hydrochloride was given every 10 minutes as indicated and electrocardiograms were also taken at the same interval. The blood pressure showed a typical rise after each injection. The electrocardiograms showed some depression of the *S T* segment and the *T* wave which was inverted in the control became upright. The heart rate first became slowed and as the doses were repeated became increased.

TABLE I.—EFFECT OF NEO-SYNEPHRIN CHLORIDE GIVEN SUBCUTANEOUSLY

Patient	Diagnosis	Neo-synephrin hydrochloride subcutaneously	Blood pressure		Heart rate	
			Control	Rise	Control	After
Miller	Thyrotoxicosis	2½ mgm.	150–60	170–90	115	86
Miller	Thyrotoxicosis	5 mgm.	146–66	186–110	111	55
Monoco	Paroxysmal tachycardia	5 mgm.	126–86	120–100	166	158
Weber	Sinus tachycardia	10 mgm.	124–78	164–96	125	66
Hough	Normal	10 mgm.	108–96	194.120	78	48
Wilson	Diabetes mellitus	10 mgm.	144–100	206–120	74	58
Becker	Allergic asthma	5 mgm.	130–90	200–110	91	60
Kmier	Allergic asthma, secondary heart failure	10 mgm.	104–76	160–96	91	60
Persons	Addison's disease	10 mgm.	86–62	110–80	133	125
Holmes	Angina	10 mgm.	130–56	188–66	90	70
Franklin	Auricular fibrillation	10 mgm.			130	85

The effect of neo-synephrin hydrochloride subcutaneously on the blood pressure and pulse in a number of patients with cardiac damage. There was a rise in blood pressure and a fall in heart rate in all cases except one. Electrocardiograms were taken during the course of these experiments and showed no significant changes as a result of the drug except the slowing of the heart rate.

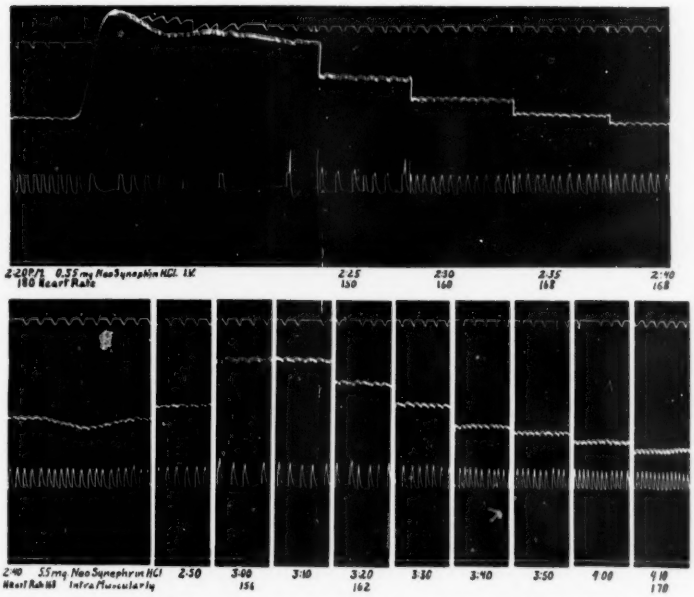

Fig. 4. The comparative effects of an intravenous and a subcutaneous injection of neo-synephrin in a 5.5 kilogram dog anesthetized with sodium barbital (.25 gram per kilogram intraperitoneally). The upper record is blood pressure and the lower is respiration. The upper graph shows the effects of an intravenous injection of 0.1 milligram per kilogram of neo-synephrin hydrochloride. Note the precipitous rise in blood pressure with a return to the control level in 20 minutes. The lower graph is a continuation of the upper graph and shows the effects of a subcutaneous injection of neo-synephrin hydrochloride on the blood pressure and respiration. The dose was 10 times the intravenous dose or 1.0 milligram per kilogram. Note the marked increase in blood pressure which was sustained for 1 hour and 20 minutes. In each case the heart rate and respiration decreased but increased again as the blood pressure returned to the control level.

EVALUATION OF STUDY

The use of hemodynamic drugs in the treatment of acute shock from trauma or hemorrhage is adjunctive to other supportive measures; but if it is advisable to use a hemodynamic drug, it is desirable to choose one having a large margin of safety. In two animal experiments the fatal dose from the intravenous injection of neo-synephrin hydrochloride in divided doses was 382 milligrams, and 240 milligrams per kilogram, while an adequately effective dose, as measured by the blood pressure rise, was 0.05 milligram per kilogram. The electrocardiograms taken during the course of the experiments showed no conductive disturbances and the animals did not die in ventricular fibrillation as they do with large doses of epinephrine or ephedrin. It is well known that both epinephrine and ephedrin are not well tolerated in certain types of heart disease particularly where there is an increased irritability of the cardiac musculature. As shown in Table I neo-synephrin hydrochloride was well tolerated in all the patients in which it was tried except one who had attacks of paroxysmal tachycardia and ventricular tachycardia. However, patients with thyrotoxicosis are more sensitive to the drug and seem to manifest an exaggerated response.

Neo-synephrin hydrochloride acts upon the cardiovascular system, from the subcutaneous injection, to produce a rise in blood pressure by peripheral vascular constriction and in increased stroke-volume output of the heart (see footnote, first page). The minute volume output of the heart may or may not be increased as the increased stroke output of the

CASE 1. L. D., white male, aged 60 years, private patient of Drs. Coleman and Culver was operated upon for a stricture of the urethra. The patient had presented urinary symptoms for some time, but otherwise had been in fair health.

Date	Time	Blood pressure	Pulse	Medication
10–27–35 10–28–35	10:10a.m	130/86		Transurethral resection with an electric cautery
	3:00p.m.	130/86		
	7:30	100/70		
10–29–35	9:00a.m.	86/60	78	
	10:35	76/60	78	Neo-synephrin hydrochloride—10 milligrams subcutaneously
	10:47	190/100	84	
	10:53	200/100	87	
	11:03	172/98	88	
	11:13	172/96	87	
	11:23	170/94	90	
	11:33	134/84	82	
	11:43	118/80	90	
	11:53	102/80	90	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	12:03p.m.	122/90	88	
	12:13	144/94	86	
	12:23	90/80	87	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	12:33	104/87	86	
	12:43	128/82	86	
	12:53	142/87	82	
	1:02	152/90	82	
	1:13	142/84	80	
	1:23	140/87	87	
	1:33	124/84	82	
	1:43	110/82	84	
	1-53	92/80	84	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	2:03	170/96	96	
	2:13	160/86	84	
	2:23	158/86	86	
	2:33	142/82	86	
	2:43	122/84	84	
	2:53	120/82	82	
	3:03	104/78	84	
	3:13	102/74	84	
	3:23	94/68	86	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	3:33	180/94	80	
	3:43	178/92	82	
	3:53	164/86	86	
	4:03	142/84	90	
	4:13	120/74	90	
	4:33	92/64	86	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	4:43	182/94	86	
	4:53	164/86	86	
	5:23	100/60	98	
	5:33	114/70	90	
	6:00	114/70	100	
10–30–35	6:00a.m.	120/70	104	

The patient went on to a recovery.

CASE 2. S. K., white female, aged 46 years, private patient of Dr. H. E. Jones, was admitted to St. Luke's Hospital on August 9, 1935, for a radical breast amputation. Eleven years previous a subtotal thyroidectomy had been performed, which was followed later by a recurrence. This was treated with X-ray. Three years ago she noticed a tumor in the left breast; surgery was advised, but refused. This tumor has now eroded through the skin to form a fungating mass with a purulent discharge.

Date	Time	Blood pressure	Pulse	Remarks
8–9–35		138/90	120	Admitted to St. Luke's Hospital
8–10–35	8:28a.m.			Operation started
	9:40			Operation finished
	10:00	110/80	120	Pulse weak, patient clammy Neo-synephrin hydrochloride—5 milligrams subcutaneously
	10:30	148/108	128	
	10:45	134/98	124	
	11:05	108/80	124	Pulse weak, but body warm and dry. Neo-synephrin hydrochloride—5 milligrams subcutaneously
	11:10	134/98	132	
	11:30	140/96	128	
	12:00	108/64	124	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	12:15p.m.	140/96	120	
	12:45	108/88	132	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	1:45	138/100	140	
	2:30	80/58	144	Neo-synephrin hydrochloride 5 milligrams subcutaneously
	2:45	150/100	140	

The blood pressure was sustained and the patient went on to a recovery.

CASE 3. M. C., white female, aged 42 years, was admitted to St. Luke's Hospital as a private patient of Dr. H. E. Jones, September 9, 1935, with symptoms of obstruction of the bowel. She was submitted to surgery and a large fibrous band was found to have strangulated about 3 feet of the midportion of the ileum. This portion of the bowel was resected and an end-to-end anastomosis was done between the proximal and distal portions of the ileum.

Date	Time	Blood pressure	Pulse	Remarks
9–9–35	6:40p.m.	88/?	140	Returned from the operating room in shock
	7:00	90/?		
	7:30	100/70		Neo-synephrin hydrochloride—5 milligrams subcutaneously
	7:40	106/72		
	8:00	96/78	140	
	8:30	96/78	140	
	9:00	98/76	140	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	9:15	106/78	132	
	10:10	110/86	132	
	10:30	110/84	134	

The patient went on to recovery.

heart may be compensated for by the marked slowing of the heart rate (Fig. 2 A, B). Neo-synephrin hydrochloride does not tend to produce irregular cardiac rhythms as is the case with epinephrine and ephedrin. A single subcutaneous injection usually produces a rise in blood pressure which lasts from 1 to 2 hours and this may be repeated a large number of times without much loss in hemodynamic effect and no danger to the patients. This allows time for the physician to institute other supportive measures, such as, restoring blood volume, conservation of body heat, etc. There is no question that some of the patients cited would have survived with the usual treatment of shock without using neo-synephrin hydrochloride, but it seems that patients in shock would have a better chance if the blood pressure is kept at a more normal level. Curiously enough, in these patients, the neo-synephrin hydrochloride did not cause the characteristic slowing of the pulse, and in general there was no significant change in the pulse.

SUMMARY

Neo-synephrin hydrochloride when given intravenously, intramuscularly, and subcutaneously, causes a marked rise in blood pressure and a slowing of the heart rate. The increased blood pressure from an intravenous injection lasts about 15 minutes while from a subcutaneous injection it lasts from 1 to 2 hours. The subcutaneous dose of the drug is roughly 10 times the intravenous dose, and one must be cautioned not to inject intravenously the amount of the drug which one would inject subcutaneously. (This is as true for neo-synephrin hydrochloride as it is for epinephrine). From the subcutaneous injection the rise in blood pressure is due to the increased stroke output of the heart and the marked increased peripheral vascular constriction (see footnote, first p.). The drug may be given a large number of times without much loss in its hemodynamic effect and even in large doses does not tend to produce irregular cardiac rhythms. In addition there is no evi-

CASE 4. C. B., white male, aged about 50 years, was admitted to St. Luke's Hospital on October 27, 1935, as a private patient of Dr. H. E. Jones. During a robbery the patient was shot on the lateral aspect of the right arm, the bullet coursing through the axilla, above the sternum, beneath the skin to lodge subcutaneously just lateral to the left nipple. The patient was brought to St. Luke's Hospital in shock.

Date	Time	Blood pressure	Pulse	Respiration	Remarks
10–27–35	9:15a.m.	150/100	124	24	
	9:45	142/84	116	20	
	10:15	80/60	120	20	Shock
	10:45	80/50	104	32	
	12:45p.m.	100/65	120	24	
	1:30	98/70	120	24	
	2:00	88/60	118	24	
	4:00	75/50	116	24	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	4:15	98/68	118	24	
	4:30	100/65	116	24	
	4:45	77/55	124	20	
	5:00	86/60	120	26	
	6:30	76/60	110	24	Neo-synephrin hydrochloride—5 milligrams subcutaneously
	8:00	98/60			
	11:00	112/70			
10–28–35	8:50	126/88	98	22	

The patient went on to recovery.

CASE 5. J. L., white male, aged 39 years, private patient of Dr. Duff, was admitted to St. Luke's Hospital on September 13, 1934, following an injury in which a steel plate struck his left leg and right arm. A compound fracture was present in the region of the left ankle.

Date	Time	Blood pressure	Pulse	Respiration	Remarks
9-14-35	8:00a.m.	48/?			
	10:00	66/?			Direct transfusion 500 cubic centimeters
	11:00				Synephrin tartrate cubic centimeters intravenously
	1:30p.m.	86/?		32	Neo-synephrin hydrochloride—10 milligrams subcutaneously
	3:00	94/?			
9-15-35	5:00	100/70	132	36	
	9:00	94/74	134	32	Neo-synephrin hydrochloride—10 milligrams subcutaneously
	8:00a.m.	104/76	128	30	
	12:30p.m.	112/72	132	38	
9-17-35		124/68			
9-18-35		138/88			

The patient went on to a recovery and was discharged January 31, 1935.

dence of spinal cord stimulation as measured by animal experiments or evidence of cerebral stimulation following therapeutic doses in man.

Reports have been presented in which neosynephrin hydrochloride was used as an adjunct to the usual methods of treatment in 6 patients manifesting surgical and traumatic shock.

CASE 6. A. B., white female, aged about 45 years, was admitted to St. Luke's Hospital on July 27, 1934, following an accident in which she was struck by a truck. There was a crushing injury to the right elbow which severed the brachial artery and the patient lost a great deal of blood before the tourniquet was applied. In addition there were lacerations and contusions about the body and head.

Date	Time	Blood pressure	Pulse	Remarks
7-27-34	8:30a.m.	120/74		
	9:30	72/50	114	Shock
				Neo-synephrin hydrochloride—10 milligrams subcutaneously
	9:40	84/60	108	
	9:50	84/56	112	
	9:55	86/56		
	10:00	86/60		Neo-synephrin hydrochloride—10 milligrams subcutaneously
	10:08	90/66	104	
	10:20	96/60		
	10:30	86/60	112	Neo-synephrin hydrochloride—3 milligrams intravenously
	10:40	104/70		
	10:50	80/54		
	11:00	78/50		
	11:15	50/?		
	11:30			Transfused 550 cubic centimeters blood
	6:00p.m.			Transfused 550 cubic centimeters blood
	12:00p.m.			Amputation left arm

The patient died the next day.

Although this patient died, these results show that it is possible to sustain the pressure while other methods of treatment are instituted. The patient was moribund to start with.

BIBLIOGRAPHY

1. FRAZIER, CHARLES. The modern treatment of surgical shock. J. Am. M. Ass., 1935, 105: 1731.
2. JOHNSON, CARL A. A simple dependable and portable knee jerk apparatus for use on higher mammals and man. Am. J. Physiol., 1927, 82: 75.
3. Idem. Ephedrin sulphate in the treatment of acute shock from trauma or hemorrhage. J. Am. M. Ass., 1930, 94: 1388.
4. Idem. A new device for the study of peripheral vascular phenomena in health and disease. Surg., Gynec. & Obst., 1932, 55: 731.
5. KUSCHINSKY, G., and OBERDISSE, K. Arch. f. exper. Path. u. Pharmakol., 1931, 162: 46.
6. TAINTER and STOCKTON. Comparative actions of sympathomimetic compounds. Am. J. M. Sc., 1933, 135: 832.

AN ANALYSIS OF THE MORTALITY OF GALL-BLADDER SURGERY

With a Special Note on the So Called Liver Death; Based on 404 Consecutive Surgical Cases and 100 Consecutive Surgical Deaths in the New Orleans Charity Hospital[1]

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THE surgery of biliary disease has far-reaching implications. It may begin with the gall bladder, but it by no means ends with it. The surgeon, for instance, who operates on the gall bladder operates vicariously, as it were, on the liver, and the consequences are frequently out of all proportion to the apparent ease of the surgical act. The chain of events is quite clear. Unless biliary disease is treated very promptly, it always terminates in some degree of liver damage, if indeed, as Graham and others believe, the liver damage does not precede it. Be that as it may, the liver is always involved, and the involvement is always potentially serious. The liver has enormous powers of regeneration, but some insults it cannot endure, and such insults are often initiated by the original disease and are carried beyond the point of tolerance by the surgery instituted to relieve it.

Again, while gall-bladder disease may and does occur in early life, it is pre-eminently a disease of the middle years, the years in which cardiovascular and cardiorenal and other degenerative diseases begin to take their toll. Whether those diseases occur independently or whether, as much evidence goes to prove, they are the direct consequence of the biliary disease, is not so important in this connection as is the simple fact of their existence, which in itself increases many times the risk of surgery upon such subjects.

Finally, respiratory complications are notoriously frequent in upper abdominal surgery and are particularly likely to occur in persons of middle age and later life. It must be emphasized, too, that all of these risks are over and above the risks of hemorrhage, shock, infection, and other surgical complications which are associated with any surgical procedure, however simple.

The mortality of gall-bladder surgery is much too high. Brilliant individual surgeons and exceptionally well organized clinics report mortality rates of 1 to 3 per cent, and we may take such results as our standard, but we must not quote them as if they were our own. The mortality of the average surgeon and the average mortality of all surgeons form a far truer index of the real situation. Such an index has recently been furnished by Heuer, who showed that in 36,623 cases collected from the literature the death rate was 6.6 per cent (2,453 cases), which, for all sorts of cases done by all sorts of surgeons, does not seem so bad. But a more careful analysis shows that the mortalities of the various series which make up the total vary from 2.6 per cent to 10.4 per cent, and such figures leave very little room for complacency on the part of those who are in the upper levels.

Our attention was attracted to the mortality of gall-bladder surgery by our search of the records of the Charity Hospital in New Orleans, in an endeavor to locate the cases of so called liver death following operations on the biliary system. As a by-product of that study, which has already been published in the *Archives of Surgery*, we are publishing herewith an analysis of 404 cases of gall-bladder disease for the 3 year period ending December 31, 1934, and an analysis of 100 consecutive fatal cases which have occurred in the last 8 years in this institution.

The 404 cases resulted in a mortality of 37 cases, 9.1 per cent, which is exceedingly high, but which, in all fairness, must be broken down into its component factors. Such an analysis reveals, in the first place, that the dictum that the more surgery a man does, the lower is his mortality, is sometimes fallacious and may need qualification. The whole series was done by 40 different surgeons, but the mortality in 242 cases done by 6 surgeons was 13.3 per cent (25 cases), whereas the mortality in the remaining 162 cases done by 34

[1]From the Department of Surgery of the Louisiana State University School of Medicine.

surgeons was only 7.4 per cent (12 cases). The explanation, however, is quite simple: The first group includes practically all the cases of empyema, rupture, and gangrene, many of which were desperate risks, and the mortality in it would naturally be higher than in the second group, which was composed largely of elective cases done under more favorable circumstances.

The higher female incidence, 295 to 109 cases, and the lower female mortality, 8.1 per cent to 11.9 per cent, duplicate the experience of most surgeons, though the significance of the disparity is rarely emphasized as it should be. The importance of the sex factor in biliary disease has recently been studied by Louis F. Dublin, whose figures show that the life expectancy of males after biliary surgery is considerably less than that of females, especially when stones are present. Dublin points out also that males are particularly prone to develop malignancy of the gastrointestinal tract after operations on the gall bladder.

The marked difference in this series between the negro and white incidence and the negro and white mortality is perhaps rather startling to persons who are not aware, as we are, of similar racial disparities in other surgical states. In the 404 cases there were only 59 in the negro against 345 in the white, a proportion of roughly 1 to 6, this being quite out of proportion to the negro and white hospital admissions, which are roughly 3 to 4. Furthermore, the negro mortality, 8 cases, constitutes more than a fifth of the total number of deaths, and the actual rate, 13.6 per cent, is more than 5 points higher than the white rate of 8.4 per cent. Other writers, particularly Emile Bloch of New Orleans, have called attention to the infrequency of gall-bladder disease in the negro, and to the still more marked infrequency of gall stones, but have offered no satisfactory explanation for it. Our own opinion is that the negro once possessed some true racial immunity to gall-bladder disease, which he is slowly losing, and that the high negro mortality can be explained by the fact, which can be repeatedly proved in other surgical conditions, that when once native immunity to a disease has been lost, its manifestations are likely to be more severe than they are in individuals who have never been immune. Another obvious explanation of the high negro mortality is the negro's habit of delaying medical consultation until pain and disability drive him into the hospital.

The mortality by ages, as Table I shows, is unduly high below 20 years of age, perhaps because at that period of life the disease is less frequent and less typical, and it shows a steady rise from the fortieth year onward. It is a striking fact, which has been noted by other writers also, that more than 70 per cent of the mortality of gall-bladder surgery occurs in persons over 50 years of age, although less than half of all cases occur in that age group. The distribution is not surprising, for individuals beyond middle life are frequently victims of degenerative diseases which add to the risk of gall-bladder surgery. In this series, as in most others, perforation and gangrene were more frequent in the upper age groups than in the lower ones.

The 100 consecutive deaths which we have studied in detail were assigned, after careful study of each case, to the following causes of death:

1. Peritonitis, 24 cases.
2. "Liver death" syndrome, 23 cases.
3. Pulmonary complications, 17 cases.
4. Shock and hemorrhage, 11 cases.
5. Cardiorenal complications, 10 cases.
6. Miscellaneous causes, 15 cases.

A comparison of these proportions with the proportions in the 2,453 deaths collected from the literature by Heuer, and with the 500 deaths collected by Stanton, including 100 cases he personally studied, is not very easy because of the difference in approach. In the first place, as Stanton points out, the cause of death is always merely a clinical opinion unless autopsy is done, and even autopsy does not always settle the question, though it happened to settle it in the 29 postmortem examinations done in our personal fatal series. Again, both Heuer and Stanton list as the cause of death in certain groups the pathological process originally responsible: Heuer charges 11 per cent of his fatal series to gangrene and perforation, and Stanton charges 30 per cent of his to "inherent pathology."

TABLE I.—MORTALITY BY AGE GROUPS IN 404 CASES, AND DISTRIBUTION BY AGE GROUPS IN 100 CONSECUTIVE DEATHS

	Total cases	Deaths	Rate	100 deaths Percentage
Under 20 years	7	1	14.2	2
Under 30 years	77	3	3.9	11
Under 40 years	124	6	4.8	17
Under 50 years	105	6	5.7	24
Under 60 years	57	8	14.0	25
Under 70 years	23	8	34.8	13
Over 70 years	11	5	45.4	8
Limits	9 to 78 yrs.			10 to 78 yrs.

TABLE II.—MORTALITY ACCORDING TO PATHOLOGY IN 404 CASES, AND DISTRIBUTION BY PATHOLOGY IN 100 CONSECUTIVE DEATHS

	Total cases	Deaths	Rate	100 deaths Percentage
Acute	35	10	28.6	9
Subacute	36	2	5.5	2
Chronic	294	16	5.4	58
Empyema	26	4	15.3	12
Rupture	5	3	60.0	9
Gangrene	6	0	00.0	5
Hydrops	2	2	100.0	5
Stones (all)	157	16	10.1	42
Duct stones	13	3	23.0	7
Jaundice	68	10	14.7	35
Without jaundice	336	27	8.0	65
Peritonitis	7	2	28.5	4

On the other hand, we have classified all of our cases strictly according to the immediate cause of death. Heuer classifies peritonitis, shock, and hemorrhage together, the combined figures amounting to 33 per cent. Stanton classifies them separately as we do, considering peritonitis, the responsible factor for 21.8 per cent of all deaths, and shock and hemorrhage the responsible factors for 15.4 per cent.

The most notable feature in our series is the high percentage of so called liver deaths, 23 per cent, as compared with the 4 per cent reported by both Heuer and Stanton in their collected series. It is very interesting to note, however, that this type of death constitutes 15 per cent of the 100 cases studied by Stanton personally. In our 100 fatal cases 40 per cent of the patients were rated as good risks, 20 per cent as fair, and 39 per cent as poor; 1 was moribund. It is an arresting fact that the group of liver deaths contained the highest proportion of good and fair risks found in any of the groups.

The mortality in relation to pathology in the 3 year series, and the proportionate distribution in the 100 fatal cases, are set forth in Table II, and the figures speak for themselves. One fact should be stressed—that in 4 of the 100 fatal cases the duct stones were discovered only at autopsy, which suggests that they existed in a similar proportion of patients not submitted to postmortem study. Such an error is not to be condoned, but it does not seem in any case in this series to have been responsible for the fatality, though had the patient lived it would most likely have caused further trouble. Lahey's figures in this connection are very striking: In recent years the incidence of exploration for duct stones has been doubled in his clinic, the result being that the incidence of stones found has also doubled, while the mortality has shown a very marked decrease.

The mortality according to procedure (Table III) reveals nothing that one does not already know. It is not surprising that the mortality of cholecystostomy should be higher than for cholecystectomy, and that the mortality for choledochostomy should be, in turn, higher than for cholecystostomy. During recent years, in the practice of most surgeons, cholecystostomy was reserved for those cases in which the condition of the patient, the extent of the disease, or the desire to preserve the gall bladder for possible future surgery, contra-indicated its removal. Gelpi's figures from the New Orleans Charity Hospital for 476 cases done between 1914 and 1925 prove this point quite clearly. In that series, when cholecystectomy and cholecystostomy were used almost interchangeably, the mortality for the two procedures was practically identical. With the recent renewal of the debate as to whether cholecystostomy is not the safer procedure, it may be that the figures for the next few years will reverse those we are now reporting.

TABLE III.—MORTALITY ACCORDING TO PROCEDURE IN 404 CASES, AND DISTRIBUTION ACCORDING TO PROCEDURE IN 100 CONSECUTIVE DEATHS

	Total cases	Deaths	Rate	100 Deaths Percentage
Cholecystectomy	331	20	6.0	55
Cholecystostomy	50	9	18.0	32
Choledochostomy	20	6	30.0	11
Other procedures	3	2	66.6	2
Drainage	66	11	16.6	47
Appendectomy also	129	8	6.2	19

Dublin, in the study referred to, notes that the late death rate after removal of the gall bladder is only 95.9 per cent of the expected rate, whereas after drainage it is 155.7 per cent, and after drainage for stones it is 214.9 per cent. The mortality by sexes after drainage is equally striking, being 233.3 of the expected rate for men, but only 65.6 per cent for women. These figures lend further significance to the fact that, in the 100 fatal cases which we have studied, 8 patients had previously been submitted to cholecystostomy, as had 18 patients, 1 of whom died, in the 3 year series.

In this community, drainage is very frequently not done after cholecystectomy for uncomplicated disease unless some special indication exists, and it is not surprising, therefore, to find the mortality for drained cases in this study materially higher than for the cases not drained. Nor is it surprising to find in the 100 fatal cases that in only 30 was cholecystectomy done without adjunct procedures, or to find that drainage was done in 47 cases. In the 129 cases in the 3 year series in which appendectomy was done in addition to the gall-bladder operation, the mortality was almost 3 per cent lower than the mortality for the whole series (6.2 per cent against 9.1 per cent), and appendectomy was done in only 19 of the 100 fatal cases. Clearly this procedure is reserved for those patients whose condition is assumed to be good enough to warrant the slight added risk entailed in removing a structure whose continued presence holds potentialities of trouble from the cradle literally to the grave.

The anesthetic factor is usually of no particular importance from the standpoint of mortality. On certain services, unless contraindications exist, spinal analgesia is routine, just as on certain others general anesthesia is routine, and in the 3 year series the mortality is almost the same, 8.3 per cent for spinal against 8.5 per cent for ether. In the fatal cases ether was used in 35 and spinal in 48, which may be of some significance, for an unwisely administered spinal anesthetic is possibly more dangerous than an unwisely administered ether anesthetic. The mortality for local analgesia, 50 per cent in 4 cases, and for ethylene anesthesia, 12.5 per cent for 16 cases, is no reflection on either variety of anesthesia: in this hospital the mere fact that these agents were employed means that the patients were considered doubtful risks.

In all studies of gall-bladder surgery, the vexed question of the immediate versus the deferred operation demands consideration, and, as was pointed out in the symposium on the subject held by the American Surgical Association in 1933, there is excellent authority for either point of view, especially when such men as J. M. T. Finney, Sr., and Dean Lewis are on opposite sides of the debate. Harvey Stone's argument is naturally beyond refutation, that there may be some gifted diagnosticians who can tell when an acute process will subside and when it will go on to perforation and gangrene, but he is not among them and he has no regrets about it either. Equally beyond contradiction is his further argument that whether or not a surgeon possesses the skill necessary to handle a difficult acute case has nothing to do with the matter, since it is not a sound policy to compromise principles of treatment to suit an assumed deficiency of skill in the profession.

But other things must also be considered. There is a rather frequent tendency among the advocates of the immediate operation to argue in generalities, and to charge all cases of empyema, perforation, gangrene, and peritonitis against the conservative type of treatment. This is far from the truth, at least if the Charity Hospital figures are representative, as we believe they are. Of the 26 cases of empyema, gangrene, and rupture in the 100

deaths which we studied, only 5 were in patients in whom operation had been delayed in the hospital; in the other 21 the blame must be put upon the patients who delayed seeking medical treatment until they had reached this state, for in them all operation was done as an emergency measure as soon as they were admitted.

It would be well, it seems to us, if all the statistics of biliary surgery were made up so that uncomplicated and complicated acute cases could be discussed separately. It is hardly fair to discuss complications which existed before the surgeon saw the patient as if they were his responsibility and had occurred under his eye. It stands to reason that the competent and intelligent surgeon will not continue to employ expectant treatment beyond a certain time if he sees that it is not successful. On the other hand, a very strong argument in favor of immediate operation is the fact that serious complications are not always recognized beforehand. In one of the delayed cases in our series, for instance, rupture was not suspected until operation was done, and in 7 cases in the series reported by Judd and Phillips it was not suspected until autopsy. Be that as it may, the mortality for operation in the acute stage in this series, as in most reported series, is still considerably higher than the mortality for the interval operation, and in our opinion the last word is still to be said on the subject.

Pulmonary complications are exceedingly disturbing, for they follow all types of anesthesia here as elsewhere. In the 17 cases included in our series of fatalities, the anesthetic agent was spinal in 7 cases and local in 2, which would seem to lift from ether anesthesia much of the onus which it has had to bear in this connection. Indeed, there is no longer any doubt that the responsibility for such complications must be charged against surgical procedures in the upper abdomen rather than against the anesthesia used in their performance. After such operations the vital capacity is reduced, the chest expansion is limited, and more or less atelectasis is almost always present. We personally agree with Stanton that the high incidence of pulmonary embolism which he found in his collected series, and which is at variance with his personal experience, suggests that the authors reporting the cases were perhaps rather partial to that diagnosis. Embolism does not appear as a cause of death in our own fatal series, and we have been impressed, in a study now in progress of the surgical autopsy material in Charity Hospital, with the actual rarity of this complication, particularly as compared with the tendency of most internes—and of all too many practicing surgeons—to explain all cases of sudden death by it.

The high incidence of cardiorenal complications in biliary disease is to be explained partly by the age at which this disease occurs most frequently, and partly as a cause and effect relationship, for which strong proof is furnished by the improvement so often apparent in the cardiac condition after the biliary infection is eliminated. Whether or not this be true, it is easy to see how the sudden development of a serious infectious process may throw upon an already damaged heart a burden which it can scarcely bear, and how the added strain of surgery may be the straw that turns the tide. Such damage, too, is likely to be irreparable, as Judd and Priestley have shown in an analysis of 65 late deaths after gall-bladder surgery, in which cardiac disease and apoplexy were responsible for 45 per cent, whereas normally they would be responsible for not more than 20 per cent.

The incidence of hemorrhage as a cause of death in jaundiced patients is surprisingly small in this hospital. Seven of the 11 patients in the shock and hemorrhage group died of shock; of that there is no possible doubt. Of the 4 remaining, the first patient perhaps died of shock but more probably as the result of the spinal anesthetic; he collapsed at the end of the operation and died on the table. The second patient lost a moderate amount of blood on the table, when an anomalous artery was cut, considerable trauma being inflicted before the bleeding was controlled; she died 10 hours after operation, perhaps of hemorrhage, more probably of shock. The third patient took a sudden turn for the worse 18 hours after operation, and died 3 hours later; the clinical signs pointed to deferred shock, but as autopsy was not permitted it may be

that hemorrhage was present. The fourth patient, a badly jaundiced negro male, who was still regarded as a very poor risk after scrupulous pre-operative preparation, did not lose an undue amount of blood at operation and left the table in fairly good condition. An hour after his return to the ward he fell out of bed, and he died 2 hours later. At autopsy the exact origin of the blood in the abdomen could not be determined, and it may be that death was due to trauma rather than to continued oozing. Even if the last 3 fatalities are charged against hemorrhage, the percentage of such cases is still very small, and is in decided contrast to Walters' generally accepted dictum that 50 per cent of all patients with jaundice die of hemorrhage. It is likewise in contrast to Stanton's figures, which show that in 42 deaths due to cholemia, hemorrhage was a feature in 20, or almost half.

Miscellaneous causes of death in this series include such conditions as mesenteric thrombosis associated with pancreatic necrosis; shock following the resuture of a partially eviscerated wound; deprivation of bile as the result of biliary fistula, in one case associated with hypoglycemia; renal failure, not to be confused with the type of renal failure seen in the liver death syndrome; acute gastric dilatation; cerebral hemorrhage; intestinal obstruction; subphrenic abscess, which was drained 2 days antemortem; staphylococcal septicemia; cirrhosis of the liver. In 1 case no cause of death could be determined clinically and autopsy was not permitted. Stanton believes that cholangitis or liver abscess is frequently overlooked as a cause of death, and he thinks also that subphrenic abscess, which is rarely recognized clinically, is rather more frequent that is suspected. How many cases of the latter condition are overlooked at Charity Hospital we have no way of knowing, but as far as proof by operation or autopsy is concerned, it is our impression, based on a careful study of many records, that it is suspected in this institution decidedly more frequently than it is proved.

We have purposely reserved until the last the group of 23 so called liver deaths, which form a unique feature of this special study and which constitute a higher percentage of such deaths than is noted in most other studies. This group of cases has recently been studied exhaustively in two previous publications (Boyce and McFetridge), and the following summary is taken from those papers, in the first of which 20 cases are analyzed and in the second of which the number is raised to 23.

It should be emphasized in the beginning that these cases were selected with the utmost care. In the 100 fatalities studied, there were several other cases in which a similar cause of death might reasonably have been presumed —a point which Stanton also makes in his discussion of 15 such cases in his own series—but because some other factor was present which might confuse the situation we omitted all of them from the analysis.

Group 1A consists of 8 cases in which death occurred within 48 hours after operation, with hyperpyrexia as the only notable symptom. The patients, whose ages ranged from 36 to 58 years, all gave a history of long standing biliary disease. Three of them were very obese and 3 had calculous gall bladders, but only 1 was jaundiced, and all of them were regarded as good or fairly good risks. Ether anesthesia was used in 6 cases and spinal analgesia in 2, and the surgical procedures were evenly divided between cholecystectomy and cholecystostomy. All had some sort of pre-operative preparation. One patient exhibited an old rupture, 1 empyema, and 1 a small patch of gangrene, but in no instance was the pathological process such as to make one anticipate a fatal result. The terminal (axillary) temperatures ranged from 105.2 to 107 degrees F. and in the 1 case in which postmortem was done the only positive finding was degenerative changes in the liver, associated with some congestion of the kidneys.

Group 1B consists of 5 cases in which death occurred within 72 hours after operation, again with hyperpyrexia as the only notable symptom. The patients, whose ages ranged from 24 to 58 years, all had a history of chronic biliary infection of many years' duration. In addition, 1 patient was jaundiced, 1 had had a previous cholecystostomy, and 2 were obese, although 2 others had lost con-

siderable weight. All were regarded as good or reasonably good surgical risks. One operation was done as an emergency immediately after admission; in all the other cases the preoperative preparation was more or less adequate. Ether was used in 2 cases, spinal analgesia in 2, and spinal and ether in the other. Cholecystectomy was done in 4 cases and cholecystostomy in the fifth. In 4 cases the gall bladder was calculous and in the fifth it was hydropic. In all instances the clinical course was the same, a fairly satisfactory recovery for 24 or 48 hours, followed by hyperpyrexia (105 to 107 degrees F. by axilla) and a rising pulse rate. The carbon dioxide combining power of the blood ranged from 24 to 38 volumes per cent. Autopsy was not permitted in any case.

Group 1C consists of 2 cases in which death occurred within 6 days after operation, the hyperpyrexia developing 24 to 48 hours antemortem, after a fairly smooth convalescence. The patients, who were 23 and 48 years old, respectively, were both good risks, although 1 was jaundiced and 1 had a gall bladder full of stones. Ether anesthesia was used in 1 case, and ethylene and ether in the other, and cholecystectomy was done in both. In both cases there was a pronounced terminal oliguria. In 1 case the previously normal non-protein nitrogen content of the blood rose to 50 milligrams per 100 cubic centimeters, and in the other the carbon dioxide combining power of the blood was 48 volumes per cent. In both cases only partial autopsy was permitted, and the kidneys, unfortunately, were not examined, but there was no evidence whatsoever of peritonitis, and the liver showed the type of necrosis evident at autopsy in the cases in group 1A.

Group 2A consists of 5 cases in which a smooth convalescence of several days was followed by oliguria, progressing to anuria, and death in uremic coma. The patients, who ranged in age from 32 to 49 years, gave the usual history of biliary infection, 2 were jaundiced, 2 had stones, 1 had empyema, 1 hydrops, and 1 a patchy gangrene. Ether was used in 1 case, ethylene and local infiltration in 2, and spinal analgesia in 2. Cholecystectomy was done in 2 cases, cholecystostomy in 2, and choledochostomy in 1. In all cases there was a postoperative rise in the non-protein nitrogen of the blood, in 1 instance to 240 milligrams per 199 cubic centimeters, and the urine showed albumin and casts not previously present. In 2 cases, as in the similar cases reported by Helwig and Schutz, the wound ruptured. In the 2 cases in which autopsy was performed there was found, in addition to the necrotic degeneration of the liver noted in the group 1 cases, a similar type of degeneration in the convoluted tubules of the kidneys.

Group 2B consists of 3 cases in which a pronounced cardiovascular collapse occurred from 60 to 92 hours after operation, with clear evidence of vasodepression, and in 1 case repeated convulsions. Oliguria was pronounced in the 2 patients who lived longest, and none lived more than 6 days after the collapse. The age range in this group was from 24 to 52 years, all the patients gave the usual history of long standing biliary disease, and although one was obese, all were regarded as good or fairly good risks. In 1 case the gall bladder was filled with stones, and operation was technically very difficult. Ether, spinal and splanchnic anesthesia were employed, and cholecystectomy was done in all cases. After operation the non-protein nitrogen content of the blood was 74 milligrams per 100 cubic centimeters in 1 case and in another 120 milligrams. Postmortem examination was not permitted in any case, but in none was there any clinical evidence of peritonitis or pneumonia.

Clinically and histologically these cases fall into two distinct groups, but beyond that no common factor is apparent. The age range is from young adult life to old age. Some of the patients were obese, but well over half of them were not, and some had lost weight. All varieties of anesthesia were employed, and in only a few instances was the pathological process such that a stormy convalescence could have been anticipated. Operation, in most cases, was fairly easy, and the great majority of the patients were regarded as good or fairly good operative risks.

The literature of liver deaths has been thoroughly reviewed in our first publication on this subject. Charles Gordon Heyd, who

originally called attention to this syndrome, has been followed by numerous other writers, most of whom report only isolated cases or very small series of cases. Connell's list, Stanton's, and our own are the largest on record. It is interesting to note, however, how much more frequently this type of death is being reported, or, more correctly, is being recognized, and for our own part, since we have become interested in the syndrome, we have developed the perhaps questionable habit of interpreting in the light of our own experience many reported cases in which the cause of death is listed as undetermined.

The various theories advanced to explain so called liver deaths are set forth at length in our first communication on the subject. The theory which we ourselves (Boyce and McFetridge) have advanced is based on a study of the 23 cases just outlined, plus a long series of experiments likewise reported in detail in our first communication. It is briefly this:

The patient with biliary disease, whether or not gross obstruction is present, always exhibits some degree of liver damage, which is not, however, incompatible with the stress and strain of ordinary life. But when surgery is undertaken, even under the most favorable circumstances, there are introduced other factors, including the anesthetic, the trauma of the surgical manipulation, the associated drop in intra-abdominal temperature, and changes in intrahepatic and biliary pressure, and with these new factors the liver, already the seat of a pathological process, cannot cope. As a result, its function promptly fails, and the toxic substances which reach it in the course of normal body metabolism are thrown off undetoxified. Then the liver cells, as they become increasingly unable to function, themselves undergo some necrotic change and themselves discharge into the circulation some additional toxic product which originates in their own degenerating cellular substance.

The next assumption follows logically upon the first. The kidney, which after the liver is the great detoxifying organ of the body, must take up the work of the liver, purely as a matter of physiology, when the detoxifying function of the latter organ fails. But in the kidney the margin of safety is very slight, and it is not fitted to handle even the normal products of body metabolism, let alone, in addition, the toxins liberated by the damaged liver cells. It promptly fails in its turn, therefore, and an overwhelming and lethal toxemia is the natural consequence.

We believe, finally, that the so called liver death or liver-kidney syndrome is a single pathological process in which the hepatic changes always precede the kidney changes. In our opinion, if the patients who die promptly with hyperpyrexia, and who exhibit liver degeneration at autopsy, could be kept alive long enough, they also would show precisely the same clinical and postmortem renal changes as do the patients who die later with typical symptoms of uremia.

Of all the theories hitherto advanced to explain the cause of death in these cases, that of Helwig and his associates, Schutz, Kuhn and Orr, is nearest our own. The difference is that they postulate a specific action of the liver toxins upon the kidney cells, a hypothesis which we consider unnecessary. We believe it only natural that the pathological process should center in the kidney, since its convoluted tubules are the normal channels of excretion for foreign proteins, which we assume these liver toxins to be. In other words, the kidney is damaged simply in the fulfilment of the abnormal duty suddenly placed upon it, or, to speak more accurately, in the fulfilment of an exaggeration of its normal duty.

We believe that by recent experimental work (Boyce and McFetridge, 3) we have eliminated changes in the biliary ducts as a possible cause of death in these cases. That such a cause could be responsible we considered unlikely from the beginning, since, as we have shown in previous communications, it is our opinion that the same syndrome is apparent in other pathological states in which the biliary ducts could not possibly play a part, these including such widely divergent pathological processes as pancreatic disease, trauma to the liver from gunshot wounds and other accidents, toxic thyroid disease, and intestinal obstruction.

Thirty-one of the patients in the 100 fatal cases had some sort of cardiac, renal, or car-

diorenal disease, and other pre-operative complications included anemia, pulmonary tuberculosis, bronchitis, bronchiectasis, parotitis, psychosis, and intestinal parasites. Twenty-seven patients were obese, which is always a factor of danger in gall-bladder surgery, and 2 were emaciated, which is just as dangerous. Five patients had lost a great deal of weight within a rather short time, in 2 cases 40 pounds each and in another 46 pounds. All 3 of these cases, for some obscure reason, fell into the liver death group.

Although in this series of fatalities there were 4 complete and 3 partial postoperative eviscerations, in only 1 instance, in our opinion, did the accident actually precipitate death. We have no desire to underestimate the seriousness of postoperative wound rupture, but a recent careful study of 44 such cases from the New Orleans Charity Hospital (Maes, Boyce, and McFetridge) has confirmed us in our opinion that the accident more frequently arises from the patient's own poor condition than itself gives rise to it. The accident is much more frequent in poor and fair risk patients than in good risks, and the mortality is almost entirely confined to the poor and fair risk groups.

The entire point of such a study as this ought to be the setting down of definite conclusions as to how the mortality of gall-bladder surgery can be reduced. Part of it, of course, is beyond the responsibility of the surgeon. When 21 of 26 patients with complicated acute disease wait to enter the hospital until their complications have developed, it is difficult to see just what the surgeon can do about it. There are already so many special diseases of which the public must be informed and against which it must be warned that it would seem almost impossible to add biliary disease to the list, other than including it in the general warning that abdominal pain is always a matter for the physician and not the lay person to handle.

Obviously, the surgeon who undertakes biliary surgery should be prepared, even in a supposedly simple case, to undertake surgery of extreme technical difficulty, and to anticipate, even in an apparently uncomplicated case, the most unexpected postoperative complications. Lord Moynihan's warning is wisely uttered. The surgery of the gall bladder, he writes, "is difficult, sometimes extremely difficult. I hold it to be of greater technical difficulty and to present more problems for immediate accuracy of judgment than any other branch of surgery. . . . If I might presume to offer any advice to the surgeon who has not had great and continued opportunities for practical work, I would suggest to him . . . to leave the surgery of the gall bladder alone." Which means, to state it bluntly, that many surgeons now doing biliary surgery should stay their surgical hands.

The choice of the proper anesthetic, which should never be ether in the presence of actual or presumptive liver damage, and the avoidance of unnecessary trauma and exposure, are important considerations. Gradual decompression of the biliary tree, by cholecystostomy, which in turn is supplemented by mechanical measures, has been suggested and has given excellent results. Pulmonary embolism is an unexpected though not very frequent complication against which it seems impossible to take precautions, but respiratory complications of other sorts can be materially reduced, as Overholt, Graham, Haggard, and others have shown, by the routine use of carbon dioxide for the first day after operation, to guard against the atelectasis which is always present and which may go on to a more serious state. Graham, in particular, advises the free use of morphine after operation, to control pain and permit free breathing, and he suggests, for the same reason, the omission of drainage whenever it is not absolutely indicated.

Patients with cardiac or cardiorenal disease should be prepared for operation in co-operation with a competent internist, and in such cases the strain of anesthesia and of surgical trauma should be reduced to the irreducible minimum. Obese patients should be slowly reduced, as suggested by Judd and Parker, and should be returned to full diet a few days before operation. Emaciated subjects should be treated by forced feedings. Anemia should be combated by appropriate measures, including transfusion if it seems necessary, and the latter measure should be employed in

cases of jaundice in which hemorrhage seems likely to occur.

It has long been recognized that the preparation of poor risk patients for gall-bladder surgery by such measures as a diet high in carbohydrates, fluids by all routes, and dextrose as necessary, orally and intravenously, will go far to reduce the surgical mortality, and recent work on the so called liver death has confirmed the importance of such preparation, and has widely extended its indications. This complication, when it does occur, always strikes as a bolt from the blue, and in the least expected cases, it is almost invariably fatal, and there seems no way to foretell and to guard against it. If the theory be correct that it is preceded by some degree of liver damage, then the obvious precaution would be to identify that damage. As yet no infallible method is available, but the best results on record are reported by Graham. Using isoiodeikon, and taking a 50 per cent retention as an arbitrary standard of safety for operation without elaborate preparation, he was able to reduce his mortality in simple cholecystectomy from 6 per cent to .4 per cent, and his mortality in common duct surgery from 7.7 per cent to 2 per cent. Regardless of how inaccurate a test may be, it is worthy of routine use if it can produce such results as these.

In the same connection, Wilensky's suggestion is of real value, that hepatic function be estimated in the light of renal function, and that evidence of renal insufficiency in cholelithiasis and kindred diseases be regarded as presumptive evidence of hepatic insufficiency. We are impressed, too, with the recent reports on the use of the hippuric acid test as an index of the state of the liver, and are at present preparing to employ it on all our gall-bladder patients.

The crux of the whole matter, it seems to us, lies in Graham's statement that the patient with a damaged liver presents a questionable risk for any sort of surgery, biliary or otherwise. That warning, taken at its face value, will mean, for all practical purposes a surgical revolution, as we have pointed out in our first communications on the so called liver death. There will be no more "simple surgery." From the standpoint of biliary surgery, the corollary is that the surgeon who proposes it must remember that hepatic disease of some degree is an invariable concomitant of biliary tract disease of any degree, and must regard all his candidates for such surgery as potentially poor risks, regardless of how incongruous their inclusion in such a category may seem.

Finally, since the catastrophes of biliary tract surgery, whatever may be their immediate cause, invariably have for their ultimate cause delay in the institution of surgical measures, there seems no logical reason for prolonged medical treatment of cholecystic disease. That does not mean the performance of cholecystectomy on insufficient indications, nor does it necessarily mean, unless one's convictions happen to lie that way, the performance of operations during acute attacks. It does seem only reasonable, however, not to allow a pathological process to continue without restraint when its end-results with delayed treatment can be as serious as the experience of every surgeon has proved them to be.

SUMMARY

1. A detailed study is made of 404 consecutive surgical cases and 100 consecutive surgical deaths from the records of the New Orleans Charity Hospital.

2. These cases are analyzed from the standpoint of age, race, sex, pathology, procedure, and cause of death.

3. Particular attention is paid to 23 cases of so called liver death, for which a new theory is advanced.

4. Methods by which the mortality of biliary surgery can be reduced are briefly outlined, again with special attention to the liver death syndrome.

BIBLIOGRAPHY

1. Bloch, Emile. Cholelithiasis in the negro. Surg., Gynec. & Obst., 1926, 43: 465–475.
2. Boyce, F. F., and McFetridge, E. M. So called "liver death." Arch. Surg., 1935, 31: 105–136.
3. Idem. The so called "liver death." An experimental study of changes in the biliary ducts following decompression of the obstructed biliary tree. Arch. Surg., 1936, 32: 1080.
4. Idem. "Liver deaths" in surgery. New Orleans M. & S. J., 1936, 88: 563–567.

5. BRYAN, W. A. Cholecystitis. South. M. J., 1929, 22: 64–69.
6. DUBLIN, LOUIS I. Factors in the selection of risks with a history of gall bladder disease. Read at Forty-Fifth Annual Meeting of the Association of Life Insurance Medical Directors of America, 1934.
7. ELIASON, E. L., and ERB, W. Mortality in surgery of the biliary tract. Ann. Surg., 1935, 101: 460–468.
8. GELPI, M. J. Analysis of postoperative mortality and postoperative morbidity in gall bladder disease. New Orleans M. & S. J., 1927, 79: 557–563.
9. GRAHAM, E. A. Lowering the mortality after operations on the biliary tract. Illinois M. J., 1931, 60: 196–202.
10. GRAHAM, H. F., and WATERS, H. S. Important factors in surgical treatment of cholecystitis. Ann. Surg., 1934, 99: 893–899.
11. HARBIN, R. M. Medico-surgical problems of gall bladder disease. Am. J. Surg., 1929, 7: 774–777.
12. HEUER, G. The factors leading to death in operations upon the gall-bladder and bile-ducts. Ann. Surg., 1934, 99: 881–892.
13. JUDD, E. S., and PARKER, B. R. Mortality following 1,324 operations on biliary system and pancreas at Mayo Clinic in 1925. Surg. Clin. N. America, 1926, 6: 1207–1231.
14. MAES, U., BOYCE, F. F., and MCFETRIDGE, E. M. Postoperative evisceration, with analysis of 44 cases. Ann. Surg., 1934, 100: 968–982.
15. MILLER, C. J. Some practical observations on gall-bladder disease. New Orleans M. & S. J., 1925, 78: 228–232.
16. STONE, H. B., and OWINGS, J. C. Acute gall-bladder as surgical emergency. Ann. Surg., 1933, 98: 760–765.
17. STANTON, E. MACD. Immediate causes of death following operations on gall bladder and ducts. Am. J. Surg., 1930, 8: 1026–1032.

CLINICAL SURGERY

FROM THE SURGICAL CLINIC, LENOX HILL HOSPITAL

TREATMENT OF CARCINOMA OF THE ESOPHAGUS

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CARCINOMA of the esophagus usually comes under a surgeon's observation when it is far advanced locally and when, as a result of malnutrition, patients have become emaciated and dehydrated, hence the treatment of this condition in most instances is limited to palliative measures. Other factors enter into this deplorable situation, namely the frequent co-existence of myocarditis, nephritis, emphysema, or arteriosclerosis, which contra-indicate an extensive operation. In addition to all this, the lesion is difficult of access and frequently irremovable because of adhesions to important surrounding vital structures, as a result of which the prognosis in operative intervention is not good. Consequently, surgeons as a rule are disinclined to operate and progress in this important field is therefore limited to the few individuals or clinics willing to do pioneering surgery against great odds.

Palliative treatment consists of measures for the relief of symptoms and for prolongation of life. The chief symptoms are difficulty in swallowing, loss of weight and strength, pressure under the sterum, backache, and pain. Loss of weight and strength are the result of esophageal obstruction and for their relief it is essential either to relieve the obstruction or to make feeding in other ways possible. Backache and pain are usually the result of involvement of surrounding structures. They are difficult to control, and symptomatic relief may be all one can hope for. On the other hand, dilatation of the stricture, X-ray treatment, or establishment of a gastrostomy with consequent relief of esophageal obstruction and the associated stagnation and irritation may bring about the desired results.

PALLIATIVE TREATMENT

Under palliative treatment the following measures may be adopted as indicated:

1. *General medical care.* In early cases when swallowing is still possible, a well balanced diet should be arranged, with all food finely divided to prevent stagnation. Attention must be given the heart and kidneys, and bowel elimination aided. Adequate rest is of importance to preserve the patient's strength. In all advanced cases the most important consideration is the administration of adequate quantities of fluids to overcome dehydration and toxemia. One may resort to hypodermoclysis, proctoclysis, or venoclysis. The addition of 5 per cent glucose to any of these is helpful. Whether to tell the patient of the nature of his illness has to be judged in the individual case. Inasmuch as most patients are men it is frequently advantageous to do so in order to gain their co-operation and to enable them to arrange their affairs. If one has the impression that such knowledge will lead to severe mental depression it may be better to withhold the information.

2. *Gastrostomy.* This should not be reserved as a last resort, but be performed in most cases soon after a diagnosis has been made. Though it is a relatively simple operation which may be done under local anesthesia with a low mortality in patients in fairly good general condition, it is much more dangerous in an emaciated dehydrated individual with poor healing power. Patients frequently object to such an operation because of the annoyance of constantly wearing a tube, and the necessity of having all food administered that way. To overcome these objections, it is recommended to do a Janeway gastrostomy which does not require the use of a tube except at meal time and which usually does not leak. After it has been in use a short time, and the esophagus has been put at rest, the swelling due to irritation associated with the carcinoma may subside and the patient be able to swallow better than before. In all complete obstructions gastrostomy is a temporary life saving measure.

3. *Dilatation.* In some clinics this method is used in preference to most others. If carefully performed by passing bougies over a previously swallowed silk thread or under guidance of the

eye through an esophagoscope, there is probably not much risk connected with it in trained hands. Unless one is an expert, however, perforation with a fatal outcome may result. It gives temporary relief only.

4. Intubation. After a carcinomatous stricture is dilated, it is at times possible to insert a tube, which maintains the lumen permanently. These tubes vary in size and are made of rubber or metal. Their introduction requires skillful manipulation and should be attempted only by experts.

5. Radiation therapy. Although classed with the palliative measures it is really intended to be more than that. One's aim is to destroy the tumor either by means of deep roentgen therapy or by the insertion of radium capsules or radon seeds. Unfortunately, such happy results have not been attained so far, but with the modern treatment developed at some clinics considerable relief and probably prolongation of life may be looked for. Radiation therapy may, of course, advantageously be employed in combination with dilatation, establishment of a gastrostomy or other treatment.

6. Electrocoagulation. In selected cases, especially those with an elevated polypoid type of tumor, destruction of the growth may at times be accomplished. One has to be very careful to select only such cases in whom the growth is small and superficial, because the destructive action of the coagulation may easily lead to perforation.

RADICAL SURGICAL TREATMENT

Because of the different problems encountered in different portions of the esophagus, it is best to consider treatment under the headings of (1) carcinoma of the cervical portion of the esophagus, (2) carcinoma of the thoracic portion of the esophagus, (3) carcinoma of the lower esophagus and the cardia.

1. Carcinoma of the cervical portion of the esophagus. The lesion may affect the esophagus alone, but it usually extends into the hypopharynx and frequently also involves the larynx. It may be impossible to say where it originated. In all such extensive cases complete extirpation of the upper end of the esophagus, the hypopharynx, and the larynx, together with associated lymph nodes, is the operation of choice. It insures thorough removal of affected tissues with a chance for permanent cure. The tracheotomy remains permanently, but the pharynx may be reconstructed later by the method advocated by Gluck with more or less successful power of deglutition. The pleural cavities are not opened. A preliminary gastrostomy should be done. Colonic

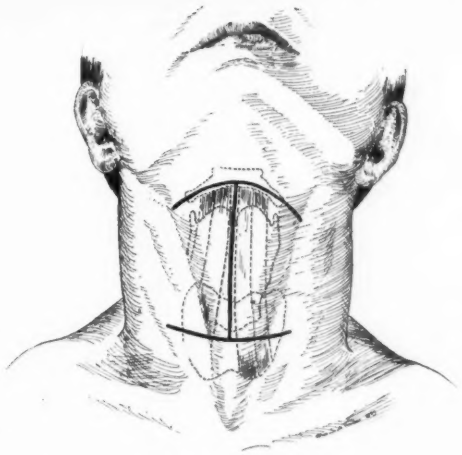

Fig. 1. Skin incision.

anesthesia is of great help, it may be supplemented through the tracheotomy after the trachea has been divided. The steps of the operation are as follows:

A transverse incision is made at the level of the hyoid bone, another one just above the clavicles, and both then are united by a median vertical incision (Fig. 1). The two skin flaps so outlined are dissected back and the sternohyoid, sternothyroid, and omohyoid muscles divided. The sternocleidomastoid muscles are retracted laterally. After this the isthmus of the thyroid gland is divided and the two lateral lobes dissected back (Fig. 2). In case there are enlarged lymph nodes, they are freed by block dissection, leaving them attached to the specimen to be removed. The larynx, trachea, pharynx, and upper esophagus are now completely freed from the spinal column. If a one stage operation is contemplated the further procedure consists of division of the trachea just below the larynx and the esophagus below the tumor (Fig. 3). Suction may be used advantageously at this time to avoid spreading mouth or tumor secretions. Strips of iodoform gauze or gauze saturated with novocain 4 per cent is immediately packed into the larynx and pharynx from below. The tracheal stump is now drawn forward and fastened into a small slit cut into the lower skin flap just above the suprasternal notch, the aim being to direct the opening forward. The esophagus stump is sutured to the margin of the skin, thus leaving a skin bridge between the two openings, which helps to prevent secretion running into the trachea (Fig. 4). Firm

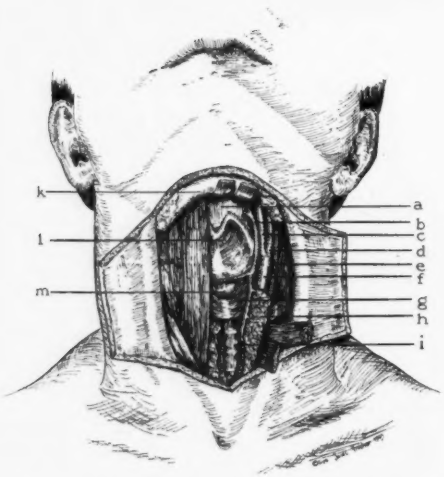

Fig. 2. *a*, Thyro-hyoid membrane; *b*, superior thyroid artery; *c*, internal carotid artery; *d*, external carotid artery; *e*, jugular vein; *f*, common carotid artery; *g*, cricothyroid muscle; *h*, thyroid gland; *i*, isthmus of thyroid gland divided; *k*, hyoid bone; *l*, larynx; *m*, cricothyroid ligament.

traction upward on the larynx and upper esophagus stump now makes further separation of the specimen from the spine easy, and after dividing the thyrohyoid membrane and the posterior

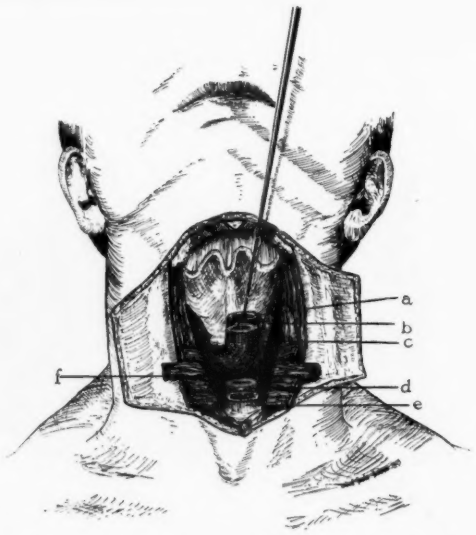

Fig. 3. The upper stumps of the divided trachea and esophagus are tilted upward. *a*, Upper stump of trachea; *b*, pharynx; *c*, upper stump of esophagus; *d*, lower stump of esophagus; *e*, lower stump of trachea; *f*, retropharyngeal space.

pharyngeal wall it may be removed. If possible, the pharynx is now completely closed above; otherwise it is closed incompletely and a small tampon inserted. Spontaneous healing takes place later. The skin flaps are now reunited and

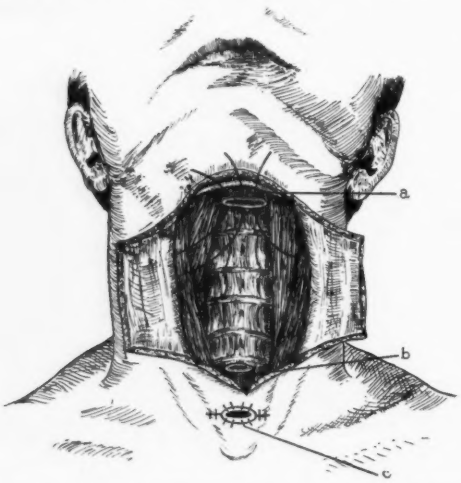

Fig. 4. Larynx and esophagus removed. *a*, Pharynx about to be closed; *b*, stump of esophagus; *c*, stump of trachea brought forward and sewed into slit of skin below esophagus.

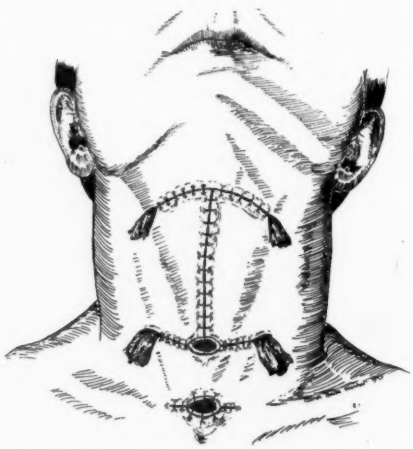

Fig. 5. Incisions closed, small gauze tampons inserted into angles of wound.

adequate drainage is established to prevent pocketing (Fig. 5). After complete recovery has taken place (Fig. 6) one may attempt reconstruction of the pharynx. The skin of the neck is used for this purpose. The pharynx is reopened. Two vertical incisions are made extending from either side of this newly made pharyngeal opening to either side of the esophagus opening, and the skin margins are united to form a tube (Fig. 7). The outer skin margins are now undermined and united over the newly formed tube as well as with the pharyngeal opening above and the esophagus below (Fig. 8).

In case the patient has been very much weakened by disease, or for technical reasons, to avoid spreading of mouth infection into the mediastinum, it may be well to divide the operation into two stages. The first stage ends with the mobilization of the entire mass to be removed. One of two courses may be followed after that. The first method consists of surrounding the mass with strips of iodoform or vaseline gauze with special reference to favoring development of adhesions downward. The skin is then closed over it. The other method consists of drawing the larynx and pharynx forward and uniting the skin flaps behind them, thus exteriorizing them. Seven to 10 days later the specimen may be safely removed and the openings cared for as described.

The operative procedure may be varied as indicated. Occasionally the tumor may be very small and limited to the upper esophagus. In such a case resection of the tumor bearing area alone may suffice. It may be possible to draw the esophagus upward sufficiently to re-establish union with the pharynx, at least posteriorly, and depend on epithelization anteriorly to give a

Fig. 6. Complete resection of larynx, upper esophagus, and hypopharynx.

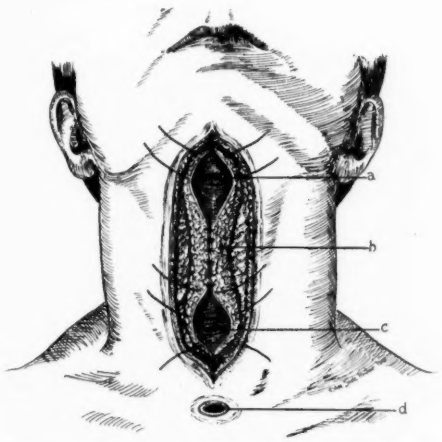

Fig. 7. Reconstruction of esophagus. *a*, Pharyngeal fistula; *b*, new skin flap about to be fashioned into a tube; *c*, esophageal fistula; *d*, tracheal stump.

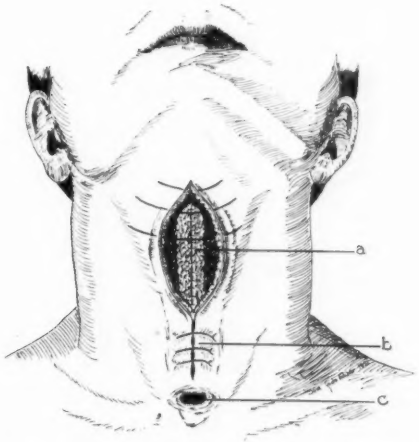

Fig. 8. Esophageal plastic finished. *a*, New esophageal tube; *b*, skin flaps sewed over tube; *c*, stump of trachea sewed into slit in skin.

Fig. 9. Incision along seventh intercostal space and extending over the seventh, sixth, fifth, and fourth ribs.

satisfactory canal. Any of these operations, however, are apt to be incomplete and may be followed by a recurrence, or contractures may take place which seriously interfere with deglutition. Therefore, the most desirable method seems to be to plan big and to follow the procedure herein outlined.

2. *Carcinoma of the thoracic portion of the esophagus.* Numerous methods have been suggested and tried but have been given up because of difficulties encountered and of unsatisfactory results. The operation which has been followed by more operative successes than any other is that devised and first performed by Torek. It is a transpleural procedure, the important points of which are a preliminary gastrostomy, wide thoracotomy for adequate exposure, division of the esophagus below the tumor with closure of both ends, drawing the upper end out at the neck through a separate incision and closure of the chest. The steps of the operation are as follows:

Under general inhalation anesthesia with differential pressure to control expansion of the lungs, the patient is placed on his right side, and an incision is made throughout the length of the seventh intercostal space. From the posterior end the incision is carried upward and the seventh, sixth, fifth, and fourth ribs divided near their

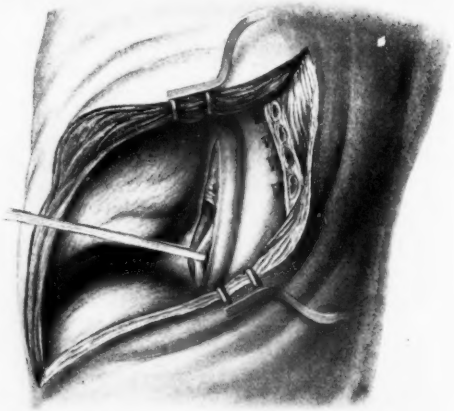

Fig. 10. Chest opened. Mediastinal pleura split and esophagus isolated.

tubercles (Fig. 9). After a rib spreader is inserted, a wide exposure is obtained (Fig. 10). In case pleural adhesions are present, they are divided, and the lung is then held aside. The pleura is now divided over the mediastinum from the lower border of the arch of the aorta to the diaphragm, and the esophagus with the tumor is identified (Fig. 10). The tumor may be located anywhere below the arch, but in our experience has been found most often behind the arch of the aorta. By careful dissection the esophagus with the tumor is freed out of its bed. This is often very difficult especially with a tumor situated behind the arch. All vessels crossing the esophagus or running into it are doubly ligated and divided. The vagus nerves are pushed away, but branches incorporated in the tumor or passing over it have to be sharply divided. A double strong silk ligature is now applied to the esophagus at a safe distance below the tumor, and the organ is divided with a cautery. The lower stump is invaginated into the remnant of the esophagus or into the stomach by means of a pursestring (Fig. 11). After incision of the pleura above the arch and the freeing of the esophagus in this location, the upper end is drawn upward from behind the arch (Fig. 12). Without difficulty the normal upper esophagus is now freed by blunt dissection as far as the neck. The chest wound is temporarily closed with towel clips and the patient's body is rotated somewhat toward the left in order to expose the neck. Great care in asepsis is required at this time in order to avoid contamination. Fresh draping is in order. An incision about 3 inches long is now made on the

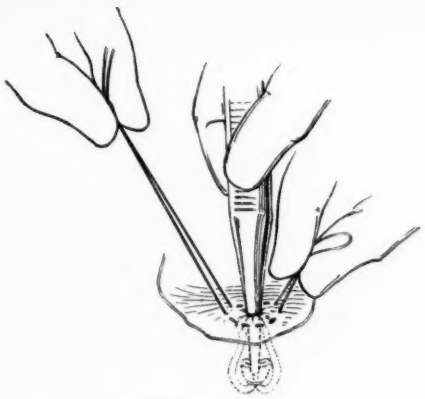

Fig. 11. The burying of the lower stump into the stomach by means of a pursestring.

left side of the neck in front of the lower border of the sternocleidomastoid and deepened in the direction toward the esophagus. About this time the patient may again be rolled more onto his side and the chest wound reopened. One hand inside, following the esophagus upward, aids greatly in identifying the esophagus in the neck. A clamp is passed down, grasps the silk ligature attached to the stump and the esophagus with the tumor is drawn out of the neck wound, wrapped in gauze and temporarily left there (Fig. 13). The tissues at once close snugly about it. The rib spreader is now reinserted and the thorax inspected. The lungs should be brought to full expansion by increasing the pressure in the bag. It has been found that this acts as the best known stimulant for the circulation. For this reason it is recommended that such expansion be resorted to from time to time during the operation, especially when the circulation is at low ebb as the result of manipulation of the esophagus behind the arch of the aorta. Before closure of the chest the mediastinal pleura is closed with continuous plain catgut suture, both above and below the arch. To prevent slipping of the divided rib ends later on, it may be well to have holes drilled before they are divided and to use them for exact approximation. However, slight overlapping does no harm. The intercostal muscles are united with continuous fine chromic catgut. The muscles of the chest wall are closed in layers with chromic catgut, and the skin with continuous plain catgut. A small, snugly fitting dressing is applied with adhesive plaster to prevent exposure of the long incision.

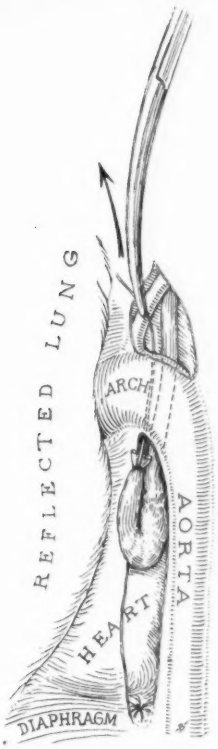

Fig. 12. Esophagus has been divided. Upper end with tumor is being drawn upward behind the arch of the aorta.

The patient is now turned on his back, and attention is directed to the esophagus stump which emerges from the neck wound. It is proposed to place the normal portion of the upper esophagus, remaining after removal of the tumor, into a subcutaneous tunnel. One therefore judges this length and makes a small transverse incision over the left anterior chest wall at this point, which usually corresponds to about the second intercostal space. A tunnel is formed bluntly and the entire specimen drawn through (Fig. 14). The tumor is now removed, leaving the esophagus stump project a short distance to allow for retraction or possible necrosis. It is fastened to the skin with a few silk sutures. After closure of the skin incision in the neck with silk sutures the operation is completed. The patient is usually in severe shock. Administration of fluids, a hot coffee enema, and possibly a transfusion are given.

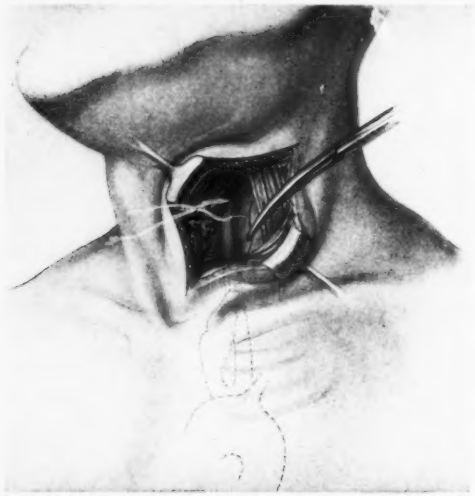

Fig. 13. Esophagus has been isolated in the neck and is being drawn out of the wound together with the tumor.

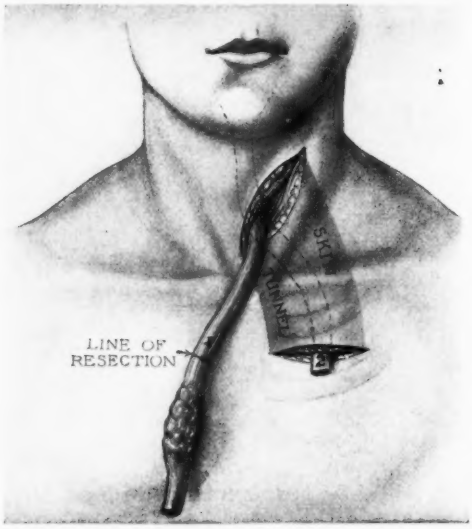

Fig. 14. Skin tunnel has been made from the lower end of the neck wound to about the region of the second intercostal space where a transverse incision has been made to which the esophagus stump will be sutured.

The question whether to drain or not to drain has to be decided in each case. It may be helpful and does no harm. A snugly fitting drainage tube is, therefore, inserted through a stab wound in the eighth or ninth intercostal space before the thorax is closed and the end of the tube is kept under fluid level. It has the advantage of permitting full expansion of the lung at the end of the operation. The lung usually remains fully expanded as can be determined by X-ray examination. The drainage tube may be removed as soon as pleural exudation ceases to develop. Gastrostomy feedings may be resumed early. However, with a view to avoid overdistention and possible leakage at the site of the inverted esophageal stump, it may be safer to delay a few days. As soon as practicable a rubber esophagus may be used connecting the upper stump with the gastrostomy (Fig. 15). In case the patient recovers, one may later consider construction of a subcutaneous esophagus from the skin of the chest wall.

3. Carcinoma of the lower esophagus and the cardia. Theoretically considered, operations for lesions in this location offer a better outlook than carcinoma of other portions of the esophagus because it is technically possible safely to implant the esophagus stump into the fundus of the stomach and thus re-establish a normal canal. No gastrostomy is required. If desired, however, it should be placed near the pylorus in order not to interfere with proper mobilization of the stomach which is essential to a successful operation. A jejunostomy may also be considered. The operation may be done from below or from above the diaphragm. Individual preference may be the determining factor, but if one considers that the abdominal operation is less shocking than the thoracic one, the former method should be chosen in suitable cases. The real deciding factor should be the position and extent of the tumor. Unfortunately, these cannot always be determined in advance. If the lesion involves the esophagus to above the diaphragm a transthoracic operation should be done. On the other hand if the cancer is confined to the cardia and encroaches but slightly on the subdiaphragmatic portion of the esophagus, sufficient mobilization may be obtained from below to make a safe suture possible. The size and rigidity of the thoracic cage also have to be considered. The abdominal approach is more suitable for women with a flexible thorax rather than for men with a large emphysematous chest.

A. Abdominal method of esophagogastrostomy. Under general inhalation anesthesia, a median epigastric incision is made which is carried upward in the notch to the left of the ensiform as far as possible (Fig. 16a). After the left lateral ligament of the liver is divided that organ is displaced to

he right and good exposure of the under surface of the diaphragm is obtained (Fig. 16). Only arely is an osteoplastic resection of the left costal rch required to get the necessary exposure. The essels of the lesser and greater curvature are now loubly ligated and divided beyond any suspicious ymph nodes. After this the stomach is divided etween clamps well below the tumor and the ower end closed by suture, while the clamp may emain attached to the upper end until the specimen is removed. If a de Petz sewing machine is available it will shorten this step of the operation considerably and aid in the preservation of asepsis. Further separation of the tumor is now continued; posteriorly it may be difficult to secure separation from the pancreas and laterally from the spleen. When finally accomplished the stomach with the tumor remains attached only to the esophagus. By passing a finger upward all around it, freeing it out of the hiatus, and at the same time making gentle traction, one may expose about 2½ to 3 inches without difficulty. This permits turning the stomach stump over and laying it on the chest wall, thus putting the esophagus on the stretch (Fig. 17). With care neither pleura is opened and no other serious damage is done. The fundus of the stomach is now drawn upward behind the esophagus as far as possible and fastened there with a few silk sutures. This places the anterior wall of the stomach in contact with the posterior wall of the esophagus. A few additional sutures are now placed on each side of the esophagus fastening it to the stomach down to the place where division is contemplated. One of two courses may be followed now, depending on whether one prefers to implant a temporarily closed esophagus stump into the stomach in the hope of thereby preserving asepsis more completely, or whether one expects to carry out a circular suture between the open esophagus stump and the stomach. In case the former method is chosen the esophagus is doubly ligated with heavy plain catgut above the tumor and divided with the cautery. The specimen is removed. A small incision is now made into the stomach opposite the esophageal stump, and the latter inserted into it and fastened snugly into place (Fig. 18). After this the stomach wall is drawn upward in front of the implantation to the level of the original sutures placed posteriorly. Sutures are now inserted between the stomach and the anterior wall of the esophagus as well as between the walls of the stomach itself until it fits firmly. An invagination of the esophagus into the stomach for a distance of 1 to 1½ inches is obtained in this way.

Fig. 15. Esophagus and gastrostomy opening connected by means of a rubber esophagus.

If one chooses to perform a suture between the open esophagus stump and the stomach similar to a gastro-enterostomy, a small incision is made into the stomach opposite the point on the esophagus where division is contemplated. The esophagus is divided and all secretions are removed by suction. Posterior sutures of interrupted fine silk are inserted through the entire thickness of both organs. If it is desired one may introduce a duodenal tube at this time (Fig. 19). It is best accomplished by passing a stomach tube up the esophagus retrograde, attaching the upper end of the duodenal tube to its lower end and by gentle traction bringing it out at the mouth. The lower end of the duodenal tube is pushed into the stomach and guided through the pylorus until it is well down into the duodenum. The suture line is now completed anteriorly, the stomach wall drawn upward over it and fastened into place as described (Fig. 20). The abdomen is closed in layers without drainage. Fluids may be administered through the tube in small quantities almost at once as there is probably no regurgitation from the duodenum into the stomach.

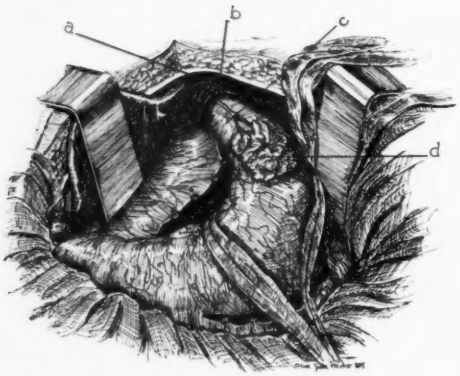

Fig. 16. Resection of lower portion of esophagus and cardia for carcinoma. The esophagus has been freed by blunt dissection and by traction upon the stomach. The thoracic portion of the esophagus has been pulled downward. *a*, Diaphragm; *b*, incision into diaphragm; *c*, esophagus; *d*, carcinoma.

B. Transthoracic method of esophagogastrostomy. The principle underlying this method is identical with that just described, and consists of resection of the tumor bearing area, followed by implantation of the esophagus stump into the fundus of the stomach. It differs from it chiefly in its approach. The operation as proposed and described in detail

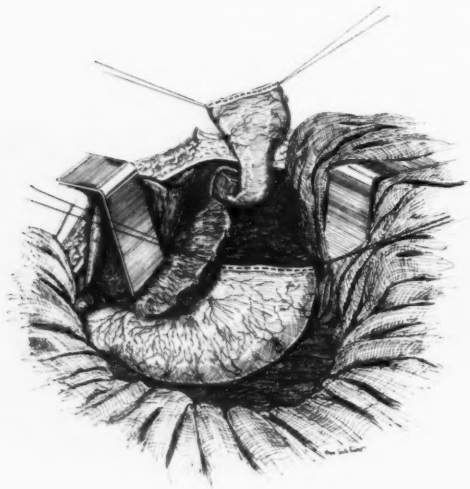

Fig. 17. Stomach divided by means of the de Petz sewing machine; upper end turned upward to permit attachment of fundus of stomach to posterior surface of esophagus.

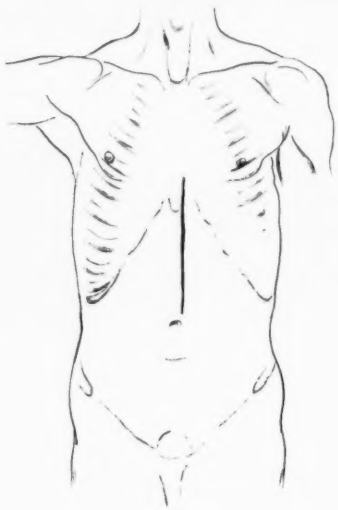

Fig. 16a. Skin incision.

by Fischer may be varied in regard to certain technical details as indicated in the individual case. In general the steps are as follows:

Under inhalation anesthesia with differential pressure, a long incision is made along the left seventh or eighth intercostal space. It may be carried upward posteriorly to permit division of one or more ribs for better exposure. The mediastinal pleura is then incised, the esophagus above the tumor is mobilized, and a tape is passed around it for traction. In order to relax the diaphragm, which facilitates the subsequent fixation of the displaced stomach, and makes the entire operation easier, the left phrenic nerve is crushed. This may be done any place in its path along the pericardium, preferably below. The diaphragm is now incised in the direction of its fibers and the incision is carried to the cardia (Fig. 21). This exposes the stomach and permits ligation of the vessels of the lesser and greater curvature. Gentle traction on the tape surrounding the esophagus, as well as traction on the stomach aids greatly in freeing the cardia as well as the tumor from their surrounding adhesions.

In case the tumor is limited to the esophagus, a double ligature may be applied above and below the tumor, the esophagus divided between the ligatures at both places and the specimen removed. The lower stump is then inverted into the stomach and the upper stump transplanted into the fundus of the stomach. However, if the tumor

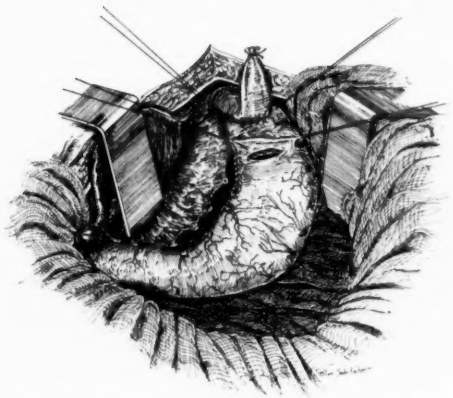

Fig. 18. Tumor removed. Esophagus stump closed, ready to be inserted into a slit made in anterior wall of stomach.

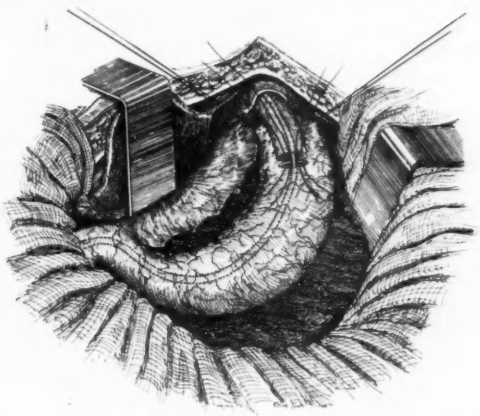

Fig. 19. Tumor removed. Esophagus stump about to be implanted into anterior wall of stomach by suture method. Duodenal tube shown which is to be used for immediate feeding.

is situated very low or if the cardia is also involved, there will not be a stump of sufficient length to permit inversion. In such cases it is necessary to take away a part of the stomach. Double clamps are therefore applied and the stomach is divided between them. The lower end is closed at once with a double row of sutures, while a clamp may be retained on the upper end. If a de Petz sewing machine is available it will be found ideal for this purpose. The esophagus is then doubly ligated and divided above the tumor, and the specimen is removed. One may, after that, proceed as described by Fischer, leaving the esophagus stump closed with a plain

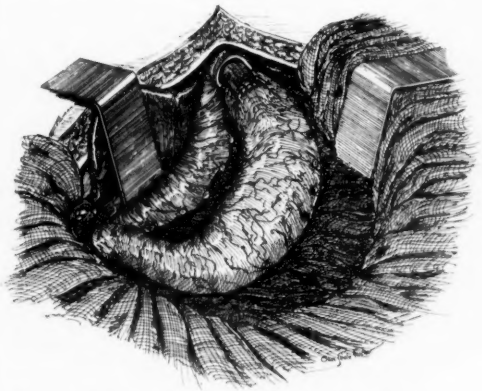

Fig. 20. Implantation of esophagus completed by drawing up the anterior wall of the stomach over the suture line and fastening it in place well up on the esophagus

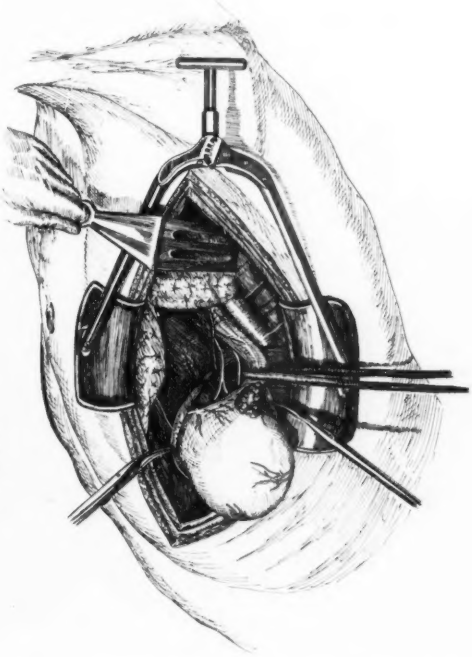

Fig. 21. Transthoracic approach with division of diaphragm for exposure of carcinoma of lower esophagus or cardia. (Drawing copied from Sauerbruch's *Die Chirurgie der Brustorgane.*)

Fig. 22. Resection of cardia with transplantation of esophagus into fundus of stomach. Specimen showing firm union.

catgut ligature, and transplanting it into the fundus of the stomach, or one may do an open anastomosis between the esophagus and the fundus of the stomach as described above under heading of "abdominal method of esophagogastrostomy" (Fig. 19). After completion of the anastomosis the edges of the diaphragm are sutured to the stomach to prevent hermiation of abdominal contents into the chest. Closed thoracic drainage may be established if indicated. The esophagus heals firmly into place as shown in Figure 22.

C. Abdomino-thoracic operation. At times it may be advisable to expose the lesion both from below and above the diaphragm. While operating from below, for instance, one may find that the lesion extends up on to the esophagus quite extensively and although it can be reached all right, a safe suture is not possible. In such cases one may add an incision upward along one of the intercostal spaces. In other cases one may deliberately plan an abdominothoracic approach. The incision described by Kirschner in his *Chirurgische Operationslehre* and illustrated in Figure 23 is recommended for the purpose. Differential pressure has to be used. The incision begins in the midline at the junction of the upper and middle third between tl.e ensiform and the umbilicus.

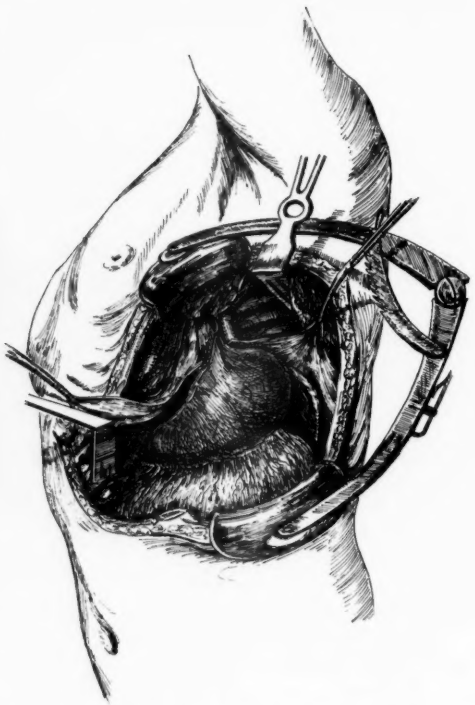

Fig. 23. Kirchner's abdomino-thoracic incision for extensive exposure of lower esophagus and cardia. (Drawing copied from *Allgemeine und spezielle chirurgische Operationslehre.*)

It runs obliquely upward over the left rectus, crosses the costal arch, and enters the seventh intercostal space, along which it is carried as far back as the angle of the rib. After the incision is deepened to the peritoneum below and the pleura above, the costal arch is divided in the line of incision. The diaphragm is now split down to the esophagus and the excellent exposure obtained permits surgical procedures on both the stomach and the esophagus. Kirschner mentions the possibility of preserving the parietal pleura intact in a suitable case and by pushing it away, carrying out the entire procedure extrapleurally.

BIBLIOGRAPHY

1. Bessessen, David H., and Bessessen, Alfred N Jr. Surgical treatment of carcinoma of the thoracic esophagus. Am. J. Surg., 1931, 437-442.
2. Eggers, Carl. Resection of the thoracic portion of the esophagus for carcinoma (first case). Arch Surg., 1925, 10:361.

3. Idem. Report of second case of carcinoma of œsophagus. Surg., Gynec. & Obst., 1930, 50:630-634.
4. Idem. Experiences with carcinoma of the œsophagus. J. Thoracic Surg., 1933, 2: No. 3.
5. FISCHER, HERMANN. Esophageal implantation into stomach after intrathoracic resection of the esophagus for carcinoma. Arch. Surg., 1926, 12:241-246.
6. Idem. Surgical treatment of the esophagus. Arch. Surg., 1923, 6-256.
7. LERCHE, WILHELM. A contribution to the etiology of cancer of the œsophagus and stomach. Surg., Gynec. & Obst., 1916, 23:42-54.
8. LILIENTHAL, HOWARD. Carcinoma of the thoracic œsophagus. Extra-pleural resection and plastic. Ann. Surg., 1921, 74:259.
9. MYERSON, M. C. Management of carcinoma of œsophagus. Surg., Gynec. & Obst., 1926, 43:690-695.
10. OCHSNER, ALTON. Anterothoracic œsophagoplasty for impermeable stricture of the œsophagus. Ann. Surg., 1934, 100:1055.
11. QUICK, DOUGLAS. Some considerations in the treatment of carcinoma of the œsophagus. Am. J. Roentgenol., 1924, May, 383-391.
12. TOREK, FRANZ. The first successful case of resection of the thoracic portion of the œsophagus in the treatment of carcinoma. Surg., Gynec. & Obst., 1913, 16:614-617.
13. Idem. The operative treatment of carcinoma of the œsophagus. Ann. Surg., 1915, 61:385.
14. Idem. The causes of failure in operative treatment of carcinoma of the œsophagus. Ann. Surg., 1929, 90:496-506.
15. WATSON, WILLIAM L. Carcinoma of the œsophagus. Surg., Gynec. & Obst., 1933, 56:884-897.

PALLIATIVE COLOSTOMY

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A MORTALITY rate totalling 13.4 per cent in 500 cases of palliative colostomy was reported recently by W. B. Gabriel, surgeon at St. Mark's Hospital, London, and O. V. Lloyd-Davies, surgical registrar to the Middlesex Hospital, London. When such a high percentage of deaths, resulting from colostomy, is reported by two of the foremost men in their field, it should convince the general surgeon and occasional operator that he should give his undivided attention to the careful consideration of each typical case before he attempts to operate.

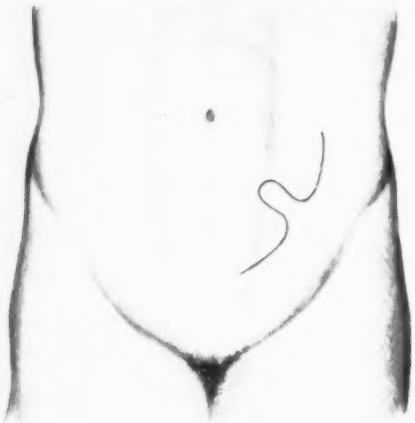

Fig. 1.

Fig. 2.

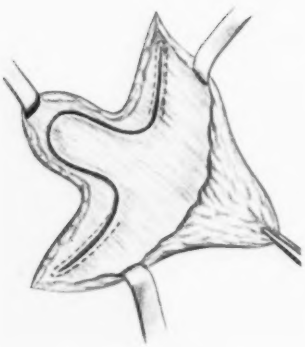

Fig. 3.

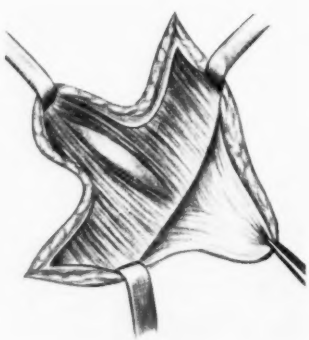

Fig. 4.

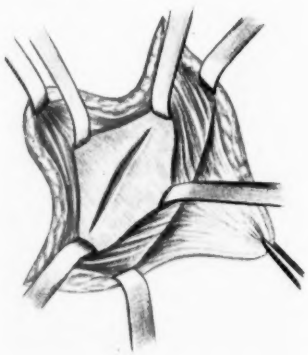

Fig. 5.

Fig. 1. Skin incision in inguinal colostomy and the outline of the tongue-shaped flap.

Fig. 2. Close-up of Figure 1. The dotted lines indicate where resection of the skin flaps may take place.

Fig. 3. Tongue-shaped incision through the aponeurosis and the dotted lines which indicate where excision of this layer may take place. The wider excision in Figures 2 and 3 is used to prevent pressure and even strangulation of the bowel drawn out for the colostomy opening.

Fig. 4. Intermuscular division in the line of the direction of the fibers in the intermuscular layers.

Fig. 5. Incision through the peritoneum.

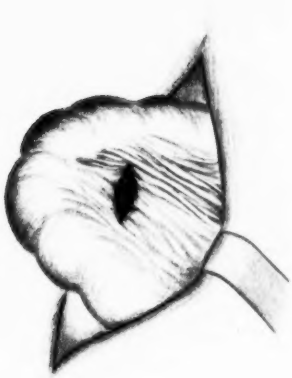

Fig. 6.

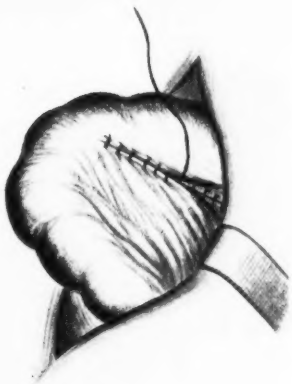

Fig. 7.

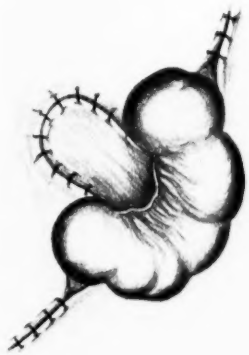

Fig. 8.

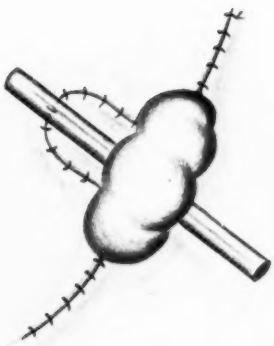

Fig. 9.

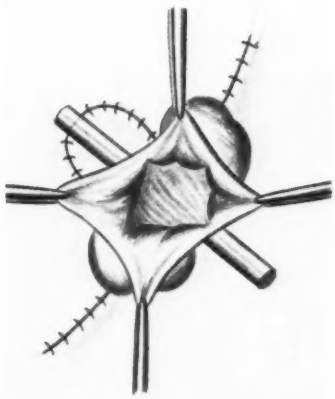

Fig. 10.

Fig. 6. Bowel drawn down from above until it meets active resistance.

Fig. 7. Two layers of suture used in the lateral peritoneal fold. The deep suture is made with No. 1 chromic gut interrupted. The superficial suture is made with Pagenstecher silk. Two sutures are used because it is a notorious fact that in carcinoma of the abdomen the peritoneal fluid dissolves suture material readily. This also fixes the bowel firmly after being drawn down from above as in Figure 6.

Fig. 8. Loop of bowel drawn out of the abdomen. The peritoneal layer has been sutured and the tongue-shaped flap of the fascia and skin is drawn through a hole in the mesentery some distance below the bowel level. The fascia is sutured with No. 2 chromic gut interrupted, and the skin with silk or silkworm gut.

Fig. 9. Glass rod $\frac{3}{8}$ inch thick and 4 or 5 inches in length inserted through the opening in the mesentery of the bowel.

Fig. 10. The bowel is opened with electric cautery after the parts have been properly protected by bird nest dressing of gauze. Experience has shown that an immediate opening gives the patient great relief from pain and relieves the distention with gas.

As far back as 1918, Killian and Kast, of our hospital staff, reported the presence of serious kidney dysfunction, in these advanced malignancies. Serious toxemias are also encountered when only a palliative colostomy has been considered.

The necessity for daily blood chemistry determinations, blood cultures, blood counts, using, preferably, the von Schilling method, and urinalysis is evident since a certain percentage of patients are so toxic that the surgeon is often obliged to postpone the performance of the colostomy until the patient is in better physical condition.

Considering the fact that this blood determination is the basis on which a decision is made as to the advisability for performing an operation, the writer does not consider it proper to have the surgeon assume the risk of operation in these serious cases of carcinoma of the colon without the benefit of this previous diagnosis. The author will present a detailed account of his pre-operative, operative, and postoperative treatment for this condition in a future publication.

The illustrations appearing in this article show the salient features of the technique. Figures 1, 2, and 9 show the tongue-shaped flap which, when sutured, strengthens the weakest portion of the incision, thereby preventing consequent bulging, herniation, and recession of the limbs of the colostomy.

Figures 7 and 8 illustrate the conclusive method for preventing herniation of the ileus and obstruction of the small intestines. A prolapse of the mucous membrane of the proximal limb of the colostomy is prevented by the pulling-down and fixation of the colon in the lateral peritoneal fold by the use of the Pagenstecher suture.

The skin and fascia edges are then resected as in Figures 2 and 3 so that no constriction of the bowel by these structures can take place. It is necessary to trim off the skin edges in order to avoid a late complication of stenosis due to fibrous tissue at the junction of the skin and mucous membrane.

The sensitiveness of the colon caused by the long-standing disease, prohibits the use of a rectal tube. When administering enemas of warm olive oil, a No. 16 or 18 French catheter is utilized.

The patients suffering from cardiovascular and pulmonary disease constitute the largest group and present the most serious possibilities after operation.

The handling of these malignancies should be avoided since pathogenic bacteria invade the peritoneal cavity following the slightest traumatism of the growth and the attached mesentery.

Local anesthesia and cyclopropane with the McGill intratracheal catheter are the methods of choice in producing anesthesia in these poor operative risks.

REFERENCES

1. Gabriel, W. B., and Lloyd-Davies, O. V. Colostomy. Brit. J. Surg., 1935, 22: 520–538.
2. Killian, J. A., and Kast, L. Some significant chemical changes in the blood coincident with malignant tumors. Proc. Soc. Exper. Biol. & Med., 1918–1919, 16: 141.
3. Myers, V. C. Practical Chemical Analysis of the Blood. p. 29. St. Louis: C. V. Mosby Co., 1924.

POLE LIGATION IN THE TREATMENT OF HYPERTHYROIDISM

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LIGATION of the thyroid arteries in goiters was first utilized by veterinary surgeons for goiters in horses. The first ligations in man are said to have been undertaken by Luigi Porta in 1811 and by Blizzard in 1813. The latter tried to ligate the superior thyroid arteries and the patient died of hemorrhage. In 1814 Walter attempted this procedure and succeeded. Early operators obtained good results in vascular and parenchymatous forms of goiter. Kocher recognized in it a means of improving highly toxic patients and used it as a measure preliminary to the more radical operation. He believed that "by ligation of one artery there is an amelioration of the patient's condition. If two are ligated, the amelioration is greater. If to this we add the removal of one lobe, the amelioration is still greater. Ligation of all four vessels will very rarely suffice to cure the patient who is seriously ill with exophthalmic goiter." We have operated upon several patients who have had both superior and both inferior thyroid arteries ligated elsewhere as a measure intended to bring about a cure of hyperthyroidism and in none of these patients had a cure resulted. We believe, therefore, that ligations should be employed always with a view of improving the patient's condition, so as to permit a subtotal thyroidectomy to be more safely performed later.

Prior to the pre-operative employment of iodine in the preparation of patients with hyperthyroidism, as proposed by Plummer, there was a great deal of discussion about when preliminary pole ligation should be employed, in what type of cases it should be used, and whether or not it brought about real improvement in these cases. Within late years, there has been but little discussion of this subject, and there is an inclination to assume that this operative procedure is no longer needed in the surgical management of severely toxic patients.

Lahey has always found that the mortality rate in the surgery of hyperthyroidism is distinctly influenced by the number of multiple stage operations done. Superior thyroid pole ligation is one of the essential steps in multiple stage thyroid operations; it is applied only to patients in the most extreme states of hyperthyroidism. Therefore it seems worth while, to ascertain and report just what the actual results are in patients submitted to this operation, to discuss some of the indications for its use, and to describe our method of ligation.

While it has always been the opinion of one of us (FHL) that if a surgeon has operated upon enough patients with hyperthyroidism it should be possible for him to put in writing a description of the type of case in which a given measure, such as pole ligation, should be employed; nevertheless, in spite of the fact that we have made the decision to do pole ligation and have done it in 119 patients in 14,000 thyroid operations, in 75 per cent of which patients have been toxic, we have always found the description of this type of case very difficult. Hyperthyroidism is such a complex state, the disease affects different individuals and different age groups in such a varying way that it becomes extremely difficult to describe clearly the type of patient in which preliminary pole ligation should be done. One could, of course, if permitted to generalize to such an extent, say that preliminary pole ligation should always be done in all those cases in which it is thought fatalities would result if right subtotal thyroidectomies were done. One could likewise logically generalize further by saying that but one superior thyroid pole should be ligated when it is thought that ligation of both superior thyroid poles might result in a fatality. As a matter of actual practice and for the purpose of maintaining in a proper attitude the minds of those of us who have to make decisions as to multiple stage operations, Lahey has always insisted that the life of a patient who dies following a complete subtotal thyroidectomy, could probably have been saved had a first stage right subtotal thyroidectomy been done; following a right first stage subtotal thyroidectomy, the patient's life would probably have been saved had a preliminary bilateral superior pole ligation been done; and it is also true that patients who could not have survived a bilateral preliminary superior pole ligation would probably have been carried successfully through a unilateral pole ligation. While these are truly generalizations, nevertheless they do help one to maintain the proper attitude toward multiple stage operations in patients seriously affected by hyperthyroidism.

The fact that we have done pole ligations in 119 patients in 14,000 thyroid operations, indicates that the number of patients who are sufficiently toxic to require that procedure are

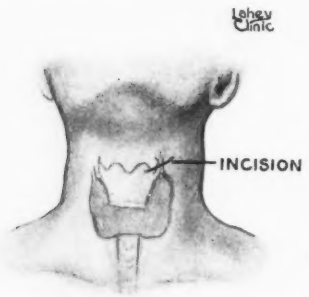

Fig. 1. Diagram of the relation of the skin incision, particularly to the upper pole of the thyroid (shown in silhouette).

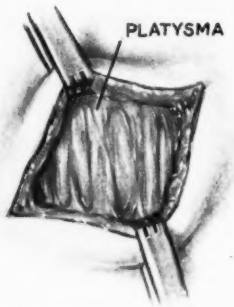

Fig. 2. The skin incision retracted and the platysma fibers presenting.

but few in proportion to the total number. However, the fact that in the entire 14,000 thyroid operations but 85 deaths occurred, and this includes deaths from cancer, from emboli, and from any other cause, makes it obvious that while the group is small as to number it is important from the surgical standpoint for the patients are extremely ill and usually desperate risks.

In these patients in spite of rest, a high carbohydrate diet, and Lugol's solution, the pulse rate remains high—160, 170, 180—gain in weight cannot be accomplished, activation is intense and the basal metabolism rate remains elevated or even increases. Of these three signs of severe hyperthyroidism, the first two are distinctly the most dependable. Pulse rates are, of course, variable, but when in the frank presence of severe hyperthyroidism the resting pulse on repeated observations is 160 or over, the question of a preliminary pole ligation must at least be seriously considered.

When in spite of a good food intake there has been a marked loss in weight and when in spite of an attempt to increase weight, the patient still loses weight, preliminary pole ligation must be given serious consideration.

Basal metabolism estimation is in general a quite accurate indication of the degree of thyroid toxicity. It can be extremely misleading, however, particularly in that not infrequently dangerous degrees of thyroid intoxication with basal rates not higher than +18 and +24 have been noted. In general, high basal rates, if true basal rates, indicate high degrees of intoxication. While the reverse—that low basal rates indicate low degrees of intoxication—is in general true, as

Fig. 3. The platysma cut and the anterior edge of the sternomastoid exposed.

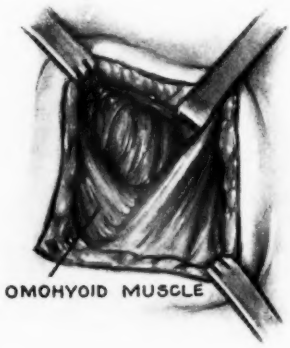

Fig. 4. The sternomastoid edge retracted and the omohyoid presenting.

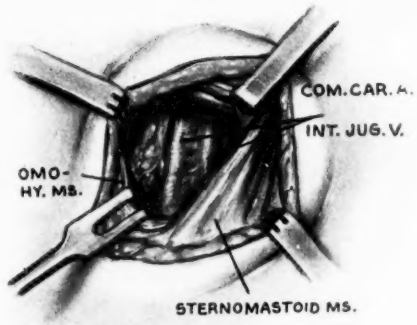

Fig. 5. The sternomastoid retracted outward, the omohyoid retracted inward, the common carotid artery and internal jugular vein showing in the depth of the wound, and the top of the thyroid with the superior thyroid artery and vein beside them.

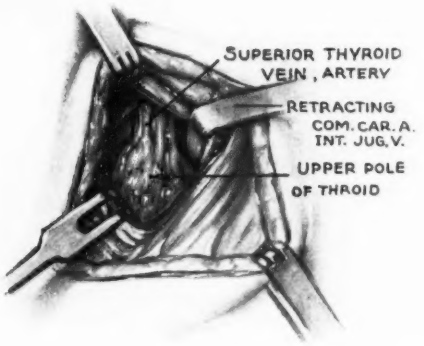

Fig. 6. The common carotid artery and the internal jugular vein have been retracted outward thus exposing the top of the thyroid gland and the superior thyroid artery and vein.

a diagnostic sign the low rates are much less dependable than the high basal rates.

For many years Lahey has believed and preached that the degree of increase in basal metabolism is a fairly good index of the degree of hyperthyroidism but that it is notably unreliable as a criterion of operability. For this reason, we would again stress that the degree of elevation of the basal metabolism is not a dependable factor upon which to make the decision for or against pole ligation. Every one who deals with hyperthyroidism cases is familiar with the patient who, in spite of all measures to improve his condition, fails to improve or even becomes worse. This is the type of patient who, in spite of the obvious risk, must be subjected to some sort of procedure which may at least temporarily check the progress of the disease; it is the type of case in which pole ligation finds its greatest usefulness.

The patient in whom preliminary pole ligations are necessary is, as a result of the primary hyperthyroidism, usually in a well advanced state of intoxication. Occasionally preliminary pole ligation will be employed in patients with toxic adenomas or secondary hyperthyroidism. However, the fact that secondary hyperthyroidism tends to occur in patients of middle age or past middle age who have less tendency to react to increase in combustion by activation makes one less apt to consider pole ligation necessary in these cases. The fact that the mortality rate of subtotal thyroidectomy in patients with toxic adenomas has always been higher than that for primary hyperthyroidism suggests the possibility that because of the lack of excessive activation, hence of caution inspiring symptoms, we have not employed multiple stage procedures in a sufficiently high percentage of patients in this group.

We have learned from our large experience with toxic thyroid states that patients who run pulse rates of 200 or over while on the operating table are in a dangerous state of intoxication. Many patients with severe hyperthyroidism while on the operating table will for a short time show pulse

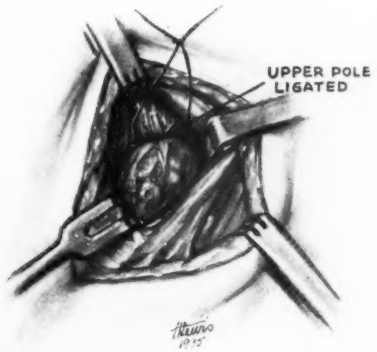

Fig. 7. The same as Figure 6 except that the first ligature about the vessels has been tied and the second one passed about the poles. Note that the pole is so ligated off the gland that no gland tissue is included in the tie.

rates of 200 or more and still not die. If, however, one were to operate on many patients with hyperthyroidism who maintained such pulse rates while on the operating table, the mortality rate would, we believe, be excessive.

In interpreting tachycardia in patients with hyperthyroidism while on the operating table it should always be remembered that there is often a preliminary rise in pulse rate as the result of the ordeal of anesthesia induction. Our anesthetists are accustomed to delay their opinion as to what the average pulse rate truly is until the patients are well past the stage of anesthesia induction and well under the anesthetic. Decisions made early in the anesthesia could well result in the performance of many more pole ligations than is actually necessary.

Pole ligations are employed in patients with the activating type of hyperthyroidism much more often than in patients with the apathetic type of hyperthyroidism and one must appreciate that the degree of activation must also influence the decision in the selection of the patient for pole ligation. In those patients who are excessively activated, this procedure must always be given serious consideration.

We realize that our statements lack tangibility insofar as we have given a definite chain of signs and symptoms which should lead one to submit the sick hyperthyroid patient to preliminary pole ligation. In this connection, we would repeat, much as we dislike to state it, that it is our opinion that no disease and no situation in surgery, where the proper decision for or against multiple stage procedures and the selection of the proper stage operation, are so dependent upon a large experience, as in the case of patients in the acute stages of primary hyperthyroidism. If one be too cautious too many unnecessary pole ligations will be done, if too reckless, too many fatalities will occur. The results of experience, which after all represent trial and error and the interpretation of the degrees of thyroid intoxication particularly, cannot be so vividly set down on paper that this experience can be accurately passed on. As the result of this large experience we would like to express our final warning. If there is doubt as to whether a preliminary pole ligation or a right first stage subtotal thyroidectomy should be done in a patient acutely ill with hyperthyroidism, the decision should always lean toward the more conservative procedure. After all, if pole ligation be done and the patient survives, but due to lack of reaction one is inclined to believe after operation that it was not necessary, all that is lost is 6 weeks of time, a recoverable matter. If a more radical procedure is employed and a fatality results, this is a non-recoverable matter and as already stated, the disturbing conviction remains that had the fatality occurred after a pole ligation, the surgeon would be in a position to be less critical of himself.

Since this paper is written with the purpose of presenting personal experiences with the hope of aiding others who may not have had such a large contact with patients of this type, we wish to speak finally of a factor which can and at times unconsciously does unfavorably influence decisions in multiple stage operations of all types and preliminary pole ligations in particularly severe cases. In most instances preliminary thyroid pole ligation is followed by a right subtotal thyroidectomy in 6 weeks and in 6 more weeks a left subtotal thyroidectomy. When preliminary pole ligation is decided upon in a given case, the surgeon is conscious of the fact that he is going to put that patient through a three stage operative procedure. He is conscious of the fact that the patient, his friends, and his family will be disappointed and possibly a little critical. He will be quite conscious of the fact that, if the patients are a long way from home, as they often are with us, it involves a long time away from home and an increased expense because of the prolongation of the hospitalization.

Sentiment for the patient and a desire on the part of the surgeon to save the patient time and money have cost many a patient his life and have no place in the decision for or against multiple stage operative procedures in a patient sick enough from hyperthyroidism to have the question of multiple stage operations raised. There would be no pleasure in the practice of surgery without sentiment, but it should be the type of sentiment which concerns primarily the protection of the patients' life and not the imprudent type concerned only in saving the patient time and money at the risk of his life. We are strongly of the opinion that decisions for or against multiple stage operations should be made with rigid disregard as to whether or not the patient ever returns for the remaining stages, as to whether or not the patient or family are disappointed or distressed, and as to whether or not it occasions financial difficulties. Only two patients in our entire experience have failed to return for final operation. After all, if the patient survives a pole ligation, he will survive in practically all instances a right subtotal thyroidectomy and then a left subtotal thyroidectomy and his living presence and improved condition will be convincing evidences that easily outweigh any argu-

ments which may be made against the soundness of this position.

The great vascularity of the gland and the very free arterial anastomosis would seem to make it theoretically improbable that a single or double ligation would materially reduce the blood supply to the gland. The main arteries are the superior and inferior thyroid arteries. These arteries anastomose freely and are not terminal arteries. The thyroid gland receives vascular supplies from the neighboring tissues such as the esophagus, trachea, prethyroid muscles, and subcutaneous tissues. This collateral supply is important because it is sufficient to prevent necrosis of the thyroid after ligation of all four thyroid arteries. Observations show that more blood passes to the thyroid through its four main arteries than to the brain through the internal carotids and vertebrals.

One of us (FHL) has often done preliminary ligation of the inferior thyroid artery, particularly in the past years before iodine was employed and when multiple stage operations were needed more often. Preliminary ligation of the inferior thyroid artery external to the large vessels and behind the sternomastoid before that vessel has divided into the transverse cervical and inferior thyroid artery, is a much more difficult operation than is ligation of the superior thyroid artery and necessitates a quite disfiguring, oblique scar of considerable length parallel to the posterior border of the sternomastoid, since it is necessary to have quite wide exposure here to identify the vessel and to avoid injury to the phrenic nerve in a cavity of considerable depth. It is, therefore, because of the fact that ligation of the superior thyroid artery can be done through relatively small transverse incisions located in the skin folds and so fairly non-obvious, that most surgeons prefer to do preliminary ligations of the superior rather than the inferior thyroid artery.

In preliminary ligation of the superior thyroid arteries, the operation is made extremely difficult if the incision is not so placed that it is directly over the point where the superior thyroid vessels enter the superior pole of the thyroid gland. One cannot say that the incision should be placed at such a fixed point as at the upper level of the thyroid cartilage. Anyone who is constantly exposing surgically the hyperplastic thyroids of patients with hyperthyroidism, is very conscious of the fact that there is a great variation in the size of these thyroid glands even in a group of patients with the same degree of toxicity. One patient in such a severe degree of hyperthyroidism that a preliminary pole ligation will be necessary will have a small firm thyroid hardly larger than a thyroid unaffected by hyperthyroidism. The next patient with hyperthyroidism may have a hard, swollen thyroid at least eight to ten times the size of a normal thyroid. In such cases, there will be a variation in the level at which the tip of the upper pole will be found, and so it is necessary that the small lateral transverse incision through which the ligation is to be done be placed over the tip of the upper pole wherever it is and not at a fixed point.

To place the incision properly, one palpates the firm apex of thyroid tissue which forms the upper pole, by pressing it against the thyroid cartilage, and places the transverse incision if possible in a skin crease directly over this point.

Because of a desire to save patients unsightly scars, there is a tendency on the part of those not experienced with this operation to attempt to do this operation through incisions which are too small. This is a great mistake. Any patient who is sick enough to need preliminary pole ligation, needs to have the operation done as expeditiously as possible and with a positive certainty that the entire pole is ligated. Any patient who is toxic enough from hyperthyroidism to require preliminary ligation of his superior thyroid poles has a tremendously increased blood supply to his thyroid gland. It is not at all unusual in patients with severe hyperthyroidism to find a plexus of veins, each vein the size of one's little finger, over the superior thyroid poles. The upper pole of the thyroid rests directly against the internal jugular vein and common carotid artery. It is, therefore, obvious that a wide exposure of these structures is desirable until one has become very familiar with the technique of superior pole ligation and even then a good sized incision and wide exposure will usually be necessary.

A transverse incision is made through the skin over the upper pole wherever it is. A small branch of the cervical plexus and one of the anterior jugular veins is often encountered. The fibers of the omohyoid and sternohyoid are separated in their longitudinal direction and the fibers of the sternothyroid are cut across for the same distance as the skin incision. This brings one directly down upon the superior thyroid pole, and it is here that one needs to be extremely careful if he wishes to avoid complicating the entire procedure (Fig. 1).

Lahey would urge upon the surgeon undertaking this operation to be certain that the entire superior thyroid artery and vein have been ligated and to do it within a relatively short operating time which demands one all important

TABLE I.—LIGATIONS DONE

Year	Pole ligations performed
1924	57
1925	1
1926	10
1927	3
1928	0
1929	0
1930	5
1931	11
1932	9
1933	3
1934	19
1935	*1

*To date, April 1, 1935.

TABLE II.—AGE INCIDENCE

Youngest, 14 years
Oldest, 72 years

Between ages	No. patients	Per cent
10 to 20 years	3	6
21 to 30 years	13	26
31 to 40 years	9	18
41 to 50 years	10	20
51 to 60 years	12	24
61 and over	3	6
	50	

thing, namely; that there be no venous hemorrhage. Once the large veins over the upper pole are torn and start bleeding, the field becomes soiled, the anatomy confused, attempts to stop the bleeding incite further bleeding and with persistent efforts in a blind field the internal jugular can easily be torn and result in a serious situation. Each dilated branch of the superior thyroid veins is gently and carefully exposed and ligated until the pulsating superior thyroid artery comes into view. The internal jugular vein and common carotid artery are then gently separated from the upper pole of the thyroid and held away from it by a special deep narrow bladed retractor. A special spiral curved ligature passer which Lahey has devised, threaded with No. 1 plain catgut is then passed downward along the lateral border of the thyroid cartilage, outward around the back of the vessels, and upward where the common carotid artery and internal jugular vein are held back by the retractor. The catgut is withdrawn from the passer and the pole is tied. The wound is inspected for bleeding, and if none is present the omohyoid and sternohyoid fibers are permitted to fall together, a few buried sutures of No. 0 catgut are put in the subcutaneous fat and the wound is closed with clips.

There are numerous theories as to how the improvement with pole ligation is obtained. Some are of the opinion that the greater part of the benefit from ligation is the result of a break in the nerve supply of the thyroid, since the principal sympathetic nerve enters with the superior thyroid arteries. These sympathetic nerves have a marked vasodilatatory and excitosecretory action upon the thyroid. It does not seem probable that there is enough diminution of the blood supply to accomplish such improvement as frequently occurs. Others believe the blood supply of the gland is diminished and, consequently, the secreting power of the thyroid is diminished. Still others believe that the benefit is due to a psychic adjustment to the operative procedures. It is impossible to arrive at any definite conclusion as to what brings about this improvement, but it is possible to ascertain in what proportion of the cases the various evidences of improvement following the operation occur.

Over a period of 11 years, from 1924 to March, 1934, there have been 119 pole ligations performed at the Lahey Clinic. During this period there were approximately 14,000 thyroidectomies performed on all types of goiters. In all of the patients having preliminary pole ligation, subsequent thyroidectomies have been performed, ligation being employed only as an operation preliminary to thyroidectomy in toxic patients.

A series of 50 patients who have had pole ligations is presented showing the effect of pole ligation on weight gain, basal metabolic rate, and pulse rate. There were 10 males and 40 females in this group, which is approximately the same ratio as the incidence of hyperthyroidism in the two sexes. The youngest in this group was 14 years of age, while 72 years was the age of the eldest. There were 22 patients between the ages of 41 and 60 years, which is 44 per cent of the total. The age incidence is given in Table II.

In the patients studied in this series, 33 or 66 per cent of the total had had the disease over 6 months, while there was a question in 5 patients as to the duration of the disease. From other studies done at the Lahey Clinic, it has been found that stage operations must be considered more often in patients who have had the disease over 6 months than in patients who have had the disease a shorter time.

Since we have always considered that duration of the disease influenced the operative risk rate, it is interesting to note that 66 per cent of these patients had had the disease over 6 months.

Weight loss is the usual history in patients with severe hyperthyroidism. When patients lose weight with hyperthyroidism, it is evidence that the excessive combustion is outrunning the

TABLE III.—DURATION OF DISEASE

	Patients	Per cent
Duration unknown	5	10
1 to 6 months	12	24
7 to 12 months	15	30
1 to 5 years	14	28
5 years plus	4	8
	50	

TABLE IV.—WEIGHT LOSS PRIOR TO ENTERING THE HOSPITAL

	Patients	Per cent
Indefinite	9	18
1 to 10 pounds	6	12
11 to 20 pounds	12	24
21 to 30 pounds	10	20
31 to 40 pounds	5	10
41 to 50 pounds	3	6
51 pounds plus	5	10
	50	

TABLE V.—EFFECT OF LIGATION ON WEIGHT, PULSE, BASAL METABOLIC RATE—50 CASES

Changes in pulse and basal metabolic rate in those who gained weight after ligation—32 cases—64 per cent.

	Pulse	Per cent	B.M.R.	Per cent
Decrease	20	62	23	72
No change	1	3	1	3
Increase	11	32	8	25

Extent of weight gain—

	Patients	Per cent
1 to 10 pounds	22	44
11 to 20 pounds	7	14
21 pounds	3	6

Changes in pulse and basal metabolic rate in those who lost weight after ligation—14 cases—28 per cent

	Pulse	Per cent	B.M.R.	Per cent
Decrease	8	57	9	64
No change	1	7	1	7
Increase	5	35	4	28

Extent of loss in weight—

	Patients	Per cent
1 to 10 pounds	11	22
11 to 15 pounds	3	6

No change in weight in 4 patients—8%

patient's ability to take in enough fuel to offset it. This, then, means that the patient is consuming himself and that a true state of thyroid crisis will result if this state continues. It is of interest, therefore, in this group to note that seventy per cent of these cases had lost ten pounds or over. Table IV gives us the weight loss of the patients prior to their entrance into the hospital.

Following pole ligations the patients were sent to their homes for a period of from 2 to 6 weeks. During this time they received Lugol's solution,

TABLE VI.—CHANGES IN PULSE RATE AFTER LIGATION

	Patients	Per cent
1. No change	2	
2. Increase—		
1 to 10	11	
11 to 20	4	
21 to 30	2	
Total	17	
3. Decrease—		
1 to 10	13	
11 to 20	9	
21 to 30	5	
31 plus	4	
Total	31	62

TABLE VII.—CHANGE IN BASAL METABOLIC RATE

	Patients	Per cent
1. No change	3	6
2. Decrease—		
1 to 10	9	
11 to 20	7	
21 plus	17	
Total	33	66
3. Increase—		
1 to 10	7	
11 to 20	5	
21 plus	2	
Total	14	28

10 minims, daily. On return for subtotal thyroidectomy, 32 patients, or 64 per cent of the total number, showed a gain in weight. (See Table V.) Of these 32 who showed a gain in weight, there was a decrease in the pulse in 20 and a decrease in the basal metabolic rate in 23 cases.

Following ligation there was a decrease in the pulse rate in 31 of the 50 patients, or 62 per cent. This closely parallels the gain in weight which occurs in 64 per cent of the total.

We found that following pole ligation there was a decrease in the basal metabolic rate in 32 cases, 66 per cent, while there was no change in 3 patients and an increase in 14 patients.

CONCLUSION

Figures showing the improvement and failure of improvement following pole ligation are submitted.

Pole ligation is still of value as a procedure preliminary to subtotal thyroidectomy in patients with hyperthyroidism who are considered too bad risks for even right subtotal hemithyroidectomy.

An attempt has been made to describe the type of patient with hyperthyroidism in whom preliminary pole ligation should be considered.

The method of ligating the superior thyroid pole which we have employed is described.

REFERENCES

1. Crile, G. W. and associates. The Thyroid Gland. Philadelphia and London: W. B. Saunders Co., 1923.
2. Crotti, A. Thyroid and Thymus. Philadelphia: Lea and Febiger, 1922.
3. Don, C. S. D. Brit. M. J., 1931, 2: 287–298.
4. Jones, E. G. Ligation of superior thyroids in patients with exaggerated toxic symptoms. South. M. J., 1921, 14: 545.
5. Lahey, F. H. Presentday surgical treatment of diseases of the thyroid gland. J. Am. M. Ass., 1925, 85: 1882–1886.
6. Idem. Multiple stage measures in surgery of severe hyperthyroidism. J. Am. M. Ass., 1922, 78: 1862–1865.
7. Pemberton, J. D. Exophthalmic goiter; indications for the stage operation. Arch. Surg., 1929, 18: 735.
8. Idem. Surgical mortality of exophthalmic goitre. New York State M. J., 1928, Mar. 1, pp. 256–261.

THE DOUBLE (DIFFERENTIAL) STETHOSCOPE

An Aid in Determining the Status of the Individual Tubes During the Performance of Rubin's Test

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ONE of the minor deficiencies of Rubin's test up to the present time has been the impossibility of determining with accuracy in every case whether a given lesion is situated in the left or the right tube and whether patency is present on one or both sides.

The criteria which have hitherto been of most value in localizing tubal lesions during the performance of Rubin's test are as follows:

1. *Pain.* Patients with normal patency complain of no significant pelvic pain. They usually experience shoulder pain on rising, but the side or sides on which the pain is experienced has been found to bear no constant relationship to the side of the tubal patency. In the presence of tubal stenosis or adhesions, pain is usually felt during the test in the region of the diseased tube and may be unilateral or bilateral. If unilateral, the differentiation between a normal and a closed tube on the opposite side is not always possible, except insofar as the presence of one normal tube tends to overshadow a lesion of the opposite side by producing a normal kymographic curve. In the presence of complete obstruction of both tubes in the region of the cornua, a typical graph is obtained and the patient complains of central abdominal pain in the suprapubic region which increases as the pressure is raised, and is entirely relieved when the pressure falls. If the obstruction is in the region of the fimbrial end of the tube, moderately severe distention pain is referred to the side on which the obstruction is present.

2. *Abdominal auscultation.* It has been customary to listen with the stethoscope over the hypogastric area during the performance of the uterotubal insufflation test. The sound of gas passing through the tubes, intermittently in normal cases, and almost continuously in the case of severely stenosed tubes, is very characteristic and clearly audible. In the presence of complete closure of one tube the sound is usually most pronounced on the side of the patent tube, but this sign is not always reliable as it is impossible, with the ordinary type of stethoscope, to listen on both sides of the abdomen at once. In discussing this question Rubin has said (3): "Auscultation, however, is not absolutely diagnostic, as the sound elicited may be transmitted to the side of the non-patent tube. The purring, hissing, or gurgling sound is, as a rule, more audible on the side of the patent tube." Speaking again as to the possibility of diagnosing patency in both tubes, Rubin has also said (2): "Unfortunately the sound is transmitted from the normal to the abnormal side so commonly as to make this physical sign unreliable for judging patency of both tubes."

3. *Vaginal palpation.* The performance of uterotubal insufflation should always be followed up by vaginal examination, particularly in those cases in which lateral pelvic pain has been complained of during the test. In case a previously undiagnosed hydrosalpinx has been distended with gas during the test, a tender swelling, not present before, will be felt on one or both sides, thus providing direct localizing evidence.

Fig. 1. Double, or differential, stethoscope used for abdominal auscultation during the performance of Rubin's test.

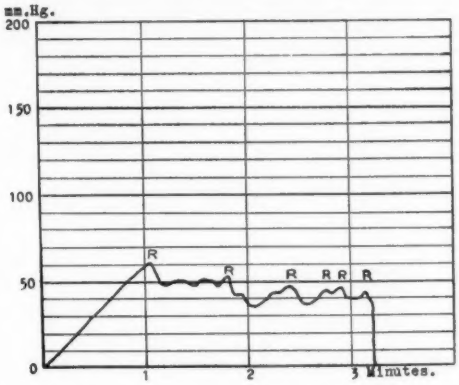

Fig. 2. Insufflation graph after left salpingo-oophorectomy for large ovarian cyst. Auscultation with double stethoscope reveals definite right sided bruit most pronounced at points marked *R*.

4. Fluoroscopy and X-ray. Just as the side upon which shoulder pain develops has been found to have no localizing significance, so the presence of unilateral or bilateral subdiaphragmatic pneumoperitoneum has been shown to bear no constant relationship to tubal patency on one or both sides. Fluoroscopy is of value in some cases, however, in demonstrating an area, or areas, of decreased density in the pelvis, corresponding with unilateral, or bilateral, tender pelvic swellings, and to be interpreted as pneumosalpinx, or, perhaps more correctly, as pneumohydrosalpinx. An X-ray film taken of such a patient in the standing position will demonstrate a localized collection of gas, limited below by a definite fluid level.

I have felt for some time that the apparently not very complex problem of differentiating with greater certainty between tubal patency on one or both sides should be capable of a comparatively simple clinical solution and that the solution probably lay in the correct use of auscultation. In considering this question my attention became attracted to the principle of the double stethoscope, and accordingly I had a trial model of the instrument illustrated in Figure 1 prepared for me. The idea of the double or differential stethoscope is by no means a new one, an instrument of this type having been first invented by Scott Alison (1) as long ago as 1858. The original purpose of the instrument was to enable sounds from different parts of the chest to be compared, but the method soon fell into disuse, and is now practically unheard of. In its proposed adaptation to the requirements of uterotubal insufflation, however, early experience seems to indicate that the double stethoscope may provide very real assistance in accurately differentiating between the status of the two tubes.

In using the instrument it is most convenient for the observer to stand on the right side of the patient, facing toward her feet, in such a position that the movements of the recording needle on the kymograph, if one is used, are plainly visible to him. The end of the stethoscope in contact with the left side of the patient's abdomen is thus connected with the observer's left ear, and that placed over her right side with his right ear. Differentiation is rendered easier if the two bells of the stethoscope are not held too close to the midline, but fairly well out toward the lower quadrant on each side.

In order, first, to test the possibility of differentiating the side of a single patent tube, a small series of patients were examined in whom it was known that one diseased tube had been removed, with conservation of the remaining healthy one. Independent colleagues, with no knowledge as to the type of operation performed, were then asked to auscultate during the performance of insufflation and to pronounce their opinion as to the

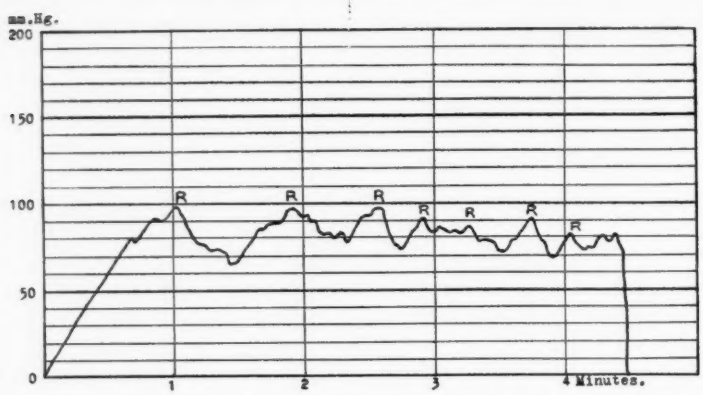

Fig. 3. Insufflation performed on thirty-eighth day after bilateral salpingostomy. The findings indicated that only the right tube was patent. Bursts of gas were heard from the right side of the instrument at the points marked *R*.

localization of the patency. In every one of 3 cases, each case being confirmed by two or more observers, an accurate pronouncement was made as to the side of the residual tube.

Figure 2 illustrates the findings in one such case.

The patient, a Chinese married woman of 33, had had a left ovarian cyst weighing 39 pounds removed on August 2, 1935. The left tube, which was much thinned and elongated, and spread out over the surface of the cyst, was, of necessity, removed also. The right tube and ovary were of normal appearance, and were left undisturbed. The patient made an uninterrupted recovery, and insufflation was carried out on the nineteenth day after operation. Auscultation with the double stethoscope showed that the bruit was definitely right sided in origin, and of intermittent character, a fresh accession of bubbling accompanying each fall in the curve at the points marked *R* on the figure.

Another example is given in Figure 3.

In this patient, aged 32, the sole complaint was primary sterility for 13 years. Examination by insufflation and lipiodol showed that both tubes were blocked, the right one at the fimbriated extremity, and the left one at the uterotubal junction. Laparotomy confirmed these findings and bilateral salpingostomy was performed, with excision of an isthmic node and tubo-uterine implantation on the left side. At the end of the operation some doubt was experienced as to whether patency on the left side could be maintained, whereas a good result was hoped for on the right side. Figure 3 shows the result of the second postoperative insufflation, carried out on the thirty-eighth day after operation. Good patency was demonstrated at a pressure under 100 millimeters' mercury, but the bruit was almost entirely right sided, only an occasional faint and fleeting bubble being auscultated over the left side. At all the peaks of the curve, marked *R*, definite bursts of gas bubbles could be heard coming from the right side. Owing to my reluctance to inject lipiodol in cases of this nature, for fear of producing a foreign body reaction, I did not feel justified in using this confirmatory procedure in this case, especially as the result obtained accorded quite closely with clinical expectation.

A third example is given in Figure 4.

This curve was obtained from a patient aged 37 complaining of one child sterility for 18 years. A slight thickening could be felt in either fornix and a clinical diagnosis was made of peritubal adhesions. At insufflation, on August 16, 1935, the patient experienced a sudden sharp pain in her right side at the point *R* in the first curve, and, coincidentally with the drop in pressure recorded at this point, a loud momentary gurgle of gas was heard through the right side of the stethoscope, lapsing into silence as the curve rose again. The pressure was released shortly after this. A second insufflation was carried out immediately afterward, and the pressure rose steadily until 180 millimeters' mercury was reached, when a sudden loud gurgle was heard on the left side, accompanied by a sudden drop in the pressure recorded at the point *L*, and the simultaneous development of severe pain in the left lower quadrant. Immediately after the gurgle marked *L* on the figure a softer bruit was heard on the right side at the point marked *R*, after which the curve rose steadily, with increasing pain in both lower quadrants, and no further auscultatory signs, until the gas pressure was released at a point somewhat above 200 millimeters mercury. The bilateral pelvic pain persisted after the termination of the test, and vaginal examination revealed two definite, tender, egg-sized swellings in the pelvis, not previously present. On rising from the table the patient felt nauseated, vomited once, and perspired freely. Fluoroscopic examination showed a complete absence of pneumoperitoneum, but revealed the presence in the pelvis of two circumscribed collections of gas corresponding in position to the swellings palpated vaginally. A film exposure, taken in the standing position, confirmed these findings and showed that each of these collections of gas was limited below by a very definite fluid level. The diagnosis in this case was unquestionably bilateral hydrosalpinx, converted into pneumohydrosalpinx by means of the insufflation test. The points *R* in the first curve, and *L* in the second curve undoubtedly represent the junctures at which the right and left tubes respectively were inflated with gas.

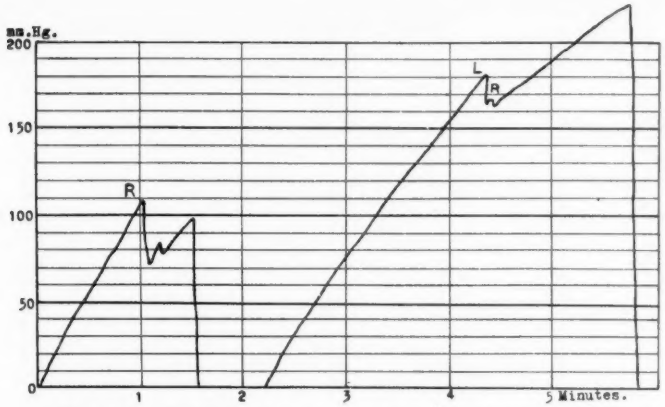

Fig. 4. Insufflation showing tubal non-patency with development of bilateral pneumosalpinx. At the point marked *R* in the first graph the right tube was heard to fill with gas. In the second graph, at the point marked *L*, the left tube similarly filled, and immediately afterward a small additional amount of gas was forced into the right tube. Fluoroscopic and X-ray confirmation was obtained.

In normal tubal patency auscultation does not play so significant a rôle, but it is possible, by the double stethoscope, to distinguish between unilateral and bilateral insufflation of gas. In the ordinary form of bilateral patency sounds are heard indiscriminately from the right and left sides of the instrument. Sometimes the peak of a contraction wave will coincide with the commencement of bubbling from one side of the pelvis, sometimes from the other, and sometimes from both sides together.

By dictating the results of auscultation to another observer, it is generally possible to label any prominent falls in the pressure graph in terms of the passage of gas through one tube or the other.

The ultimate value of the double stethoscope in determining the status of individual tubes must await the pronouncement of various observers in large series of cases, controlled by lipiodol injections and actual findings at operation. Meanwhile the method is suggested as one which present limited experience marks out as possessing distinct possibilities, especially if used in conjunction with other localizing evidence.

REFERENCES

1. Editorial. The differential (double) stethoscope. Brit. M. J., 1935, 1: 1033.
2. Rubin, I. C. Tubal strictures and their localization. Am. J. Obst. & Gynec., 1930, 20: 37.
3. Idem. Twelve years' experienece with utero-tubal insufflation. Am. J. Obst. & Gynec., 1932, 24: 566.

URINARY OBSTRUCTIONS IN INFANTS AND CHILDREN

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AMONG the triumphs of scientific urology the mastery of the urinary tract in infants and children is outstanding. Little did the physician of a few decades ago dream that, in such a relatively short time, the depths of these organs would be probed with instruments introduced through the normal excretory channels, nor that their physiological activities and pathological derangements would be revealed by the penetrating X-ray, supplemented by the administration of opaque dyes.

The development and perfection of instruments of small caliber, the striking tolerance of infants and children to instrumentation when judiciously performed, and the co-operation of the pediatrician in seeking special investigation of the urinary organs in children, creates a trinity designed to exert a tremendous influence in the development of infantile and juvenile urology.

The sole function of the excretory ducts of the urinary tract is to deliver the accumulated urine without impediment. Unfortunately, obstructive conditions along the urinary pathways are exceedingly frequent and take as their points of predilection the normal physiological constrictions: (1) the ureteropelvic juncture, (2) the intravesical ureter, (3) the internal orifice of the bladder (this the most frequent).

Stasis is a natural accompaniment of such obstructive conditions. The problem, therefore, resolves itself into one of hydrodynamics. As a result of stasis, infection is a natural expectation. These obstructive uropathies in infants contribute tremendously to infant mortality and should always be suspected in unexplainable cases of malnutrition, particularly if associated with urinary difficulties. Such suspicion may be confirmed by a determination of the nitrogenous constituents in the blood. If these are decidedly increased, a prompt urological investigation should be undertaken and the cause, which is usually obstruction, be removed at the earliest possible moment.

Bugbee and Wollstein found 117 congenital lesions of the urinary organs in infants in reviewing 4,903 necropsies performed at the Babies Hospital in New York. Fifty per cent of these were due to some form of congenital obstruction. Thus 1.2 per cent of all the infant mortality occurred as a result of obstruction either with or without infection, the most frequent location being at the internal orifice of the bladder.

Urinary infections in children are strikingly frequent. In the St. Louis Children's Hospital 1 in every 40 children either had such infections upon admission or developed them during the course of their stay. The majority of these were acute, the so called acute pyelitis, usually secondary to some focal lesion elsewhere, the most common of which were: middle ear, nasopharyngeal, pulmonary, intestinal or vaginal. Many of these acute conditions are cured following the relief of focal infections and the administration of urinary antiseptics and copious flushings. Such relief usually requires from 1 to 3 weeks. Urology at the present time is not serving its proper function with this type of acute kidney infection. Prompt ureteral catheterization with evacuation of the pelvic contents, followed by topical applications, as is currently employed in the adult, should be administered to protect the kidney substance from the ravages of infection squeezed back through it from the overcrowded pelvis which is incapable of emptying itself. The inability of the pelvis to evacuate its contents properly is in most instances not due to a pre-existing stricture but results from the acute inflammatory reaction with edema at the ureteropelvic junction secondary to the renal infection itself, a self-engendered obstruction. The longer the septic contents are allowed to remain permeating the delicate structural mechanism of the kidney, such a vital organ to human economy, the more likelihood of late scarring and irreparable damage with the formation of the framework of chronic lesions, chronic recurrent pyelitis and stone formation for years to come. In a personal communication with one of my confreres, Dr. Drennan, who is consultant at a reformatory for boys in the State of Illinois, I am informed that the presence of unsuspected pus and infection in the urine and of albuminuria and hypertension are exceedingly common and in almost every instance there has been a preceding history of pyelitis in infancy.

Chronic infections of the kidney are the ones which the urologist usually observes and those which have resisted the orthodox medical administrations. Children with such infections are never in good health. They are either persistently toxic or are subjects of recurrent intermittent infections with febrile reactions. In both instances some mechanical obstruction previously alluded to is usually the cause and must be investigated.

The persistence of medical treatment to these chronic infections was formerly due to lack of familiarity with the causative factors and to the failure of urology in offering material aid. At present, however, the remarkable curative results obtained through conservative surgical measures predict a brighter future for such afflicted subjects.

The clinical picture resulting from obstructions in the different portions of the urinary system may be very similar and the general physical signs may appear misleading. For instance, a child may present a large tender kidney and the whole symptom complex revolve around this one organ and yet the cause of this may be an obstruction in the lower urinary tract with both ureters and kidneys involved and only one manifesting the disease.

For practical purposes, and as an aid to the clinician, there are certain simple diagnostic procedures which may be helpful. First, the determination of total renal function by tests of elimination such as phenolsulphonphthalein or through tests of retention secured through a determination of the blood for its nitrogenous elements. If the total functional capacity is low, as indicated by these tests, one may be assured that both kidneys are involved regardless of the palpable evidences. Second, the determination of the presence or absence of residual urine is highly important. If residual urine is present, it is usually indicative that the condition results from obstruction at the internal orifice of the bladder and is in all probability bilateral. Third, the cystogram may afford valuable information in revealing the topographical outline of the urinary system. The fundamental lesion is at the bladder neck, if, upon filling the bladder, there is regurgitation up the ureters. Fourth, intravenous urography may be serviceable in delineating the outline of the urinary system but in my experience it has not been entirely reliable. I have seen it demonstrate normal pelves when pronounced hydronephrosis was present, and it is usually impossible to determine whether a dilatation of the ureter results from retention of excretion or regurgitation. Fifth, cystoscopic investigation of the urinary tract is usually necessary before any definite plan of corrective therapy may be satisfactorily applied, and it is indeed gratifying that children tolerate cystoscopic manipulation so admirably. Reactions are seldom observed; indeed, they occur far less frequently than with the adult, if the child is properly prepared. The infant or child with high residual urine and uremia requires the same special preliminary catheter drainage before such procedures are undertaken as is commonly employed in the adult. In hundreds of children whom I have examined, there has been but one serious reaction, and this occurred many years ago in a child who was suffering from double chronic pyelitis without obstruction.

Anesthesia is required in only 35 per cent of the cases. If one is patient with these children, secures their confidence, and allows the mother to be present with them during the examination, there is seldom any difficulty in making a complete urological investigation even in very young children without general anesthesia. If general anesthesia is necessary, it is applied only for a few moments during the instrumentation and should be removed as quickly as possible for functional studies and pyelographic determinations. The preponderance of girls over boys minimizes the necessity for general anesthesia but even in very young boys such manipulations may frequently be consummated under local anesthesia.

Obstructions at the ureteropelvic juncture are the least frequent but most destructive. Large hydronephroses or pyonephroses are the inevitable result. They are often bilateral, one side being more pronounced than the other. They are less influenced by dilatations and require either nephrectomy or some plastic surgical procedure. A two-stage nephrectomy is usually necessary for the large pyonephrotic kidneys. The preliminary drainage allows the child to be relieved of sepsis, and the secondary operation is not complicated if performed within a reasonable time. The most frequent cause of such lesions at the ureteropelvic juncture are congenital strictures and aberrant vessels, the latter offering the best chance for recovery by simple ligation of the vessel which is obstructing. For ureteropelvic stricture with extrarenal hydronephrosis with or without infection and with preservation of renal cortex, I have found the resection of the ureter with excision of the stricture and resection of the renal pelvis with reimplantation of the ureter into the dependent part of the pelvis to be the most satisfactory surgical procedure. The ureter is united to the pelvis over a soft rubber catheter splint which is brought back through the renal cortex for drainage and passed well down the ureter. Into this catheter splint numerous openings are made to allow for drainage and very few sutures are placed at the line of union, simply enough to insure stability. These should be fortified by traction sutures which are placed a goodly distance above and below the line of union. The kidney pelvis is freely drained through the cortex by means of a large catheter.

TABLE I.—ESSENTIAL FEATURES IN 26 CASES OF OBSTRUCTION

Age in Years

	Cases
Under 2	5
2 to 5	9
5 to 10	8
Over 10	4

Sex

Males	14
Females	12

Symptoms and Physical Findings

	Cases	Per cent
Frequency	13	50
Difficulty	8	
Incontinence	13	50
Pain and burning	7	
Hematuria	1	
Pyuria and pyelitis	18	69
Renal colic	3	
Uremia	8	30
Enlargement of kidney	6*	
Residual urine	21	80
Over 100 c.cm.	12	
Over 500 c.cm.	3	
No residual	2	
No note	3	

Condition at the Vesical Neck

	Cases	Boys	Girls
Contractures of the neck	9	4	5
Valves	12	6	6
Valve and lobule	1	1	0
Valve and bar	1	1	0
Villous mass and valve	1	1	0
Lobules	2	2	0

Associated Conditions

	Cases
Relaxation of sphincter	6
Trabeculation	10
Diverticulum	3
Spina bifida	5
Calculus	1
Epispadias	1
Double ureter	3
Regurgitation	12
Bilateral	8
Right	2
Left	2
Regurgitation with residual urine over 200 c.cm.	6
Regurgitation with small residual	6
Regurgitation with contracted neck	7
Regurgitation with valves	5

*5 unilateral, 1 bilateral

Obstructions at the intramural ureter are susceptible to dilatation with the catheter and many are cured in this way. Others, of a more sclerotic nature, seem best treated by the transposition operation which I described in 1919. This operation is an intravesical one requiring little manipulation and dissection. The intravesical ureter which is sclerotic and often like a pipe stem is excised from its vesical bed but its attachment at its entrance to the bladder wall is allowed to remain. This seems far superior to a ureterovesical anastomosis which is almost invariably attended by contracture, hydronephrosis, and ultimate renal death.

The most common cause of chronic pyelitis in infants and children is obstruction at the internal orifice of the bladder resulting from congenital valves or contractures. Table I and the following pages give the essential features in a series of 26 cases of such obstructions.

The importance of regurgitation of the vesical contents into the ureters and kidney pelves cannot be overestimated. It was present in 46 per cent of these cases. One-half of these occurred in the presence of a high residual urine, the remaining half with small residuals. It is evident, therefore, that the presence of a high residual is not essential for the creation of such regurgitation. Stiffening and retraction of the ureterovesical valve resulting from infection is fundamental. I have observed incompetency of the ureteral valves with large regurgitant ureters in several patients before operation, which after the relief of obstruction and subsidence of infection became competent and regurgitation did not occur.

Operations. Operations were performed on 16 of these children. Fourteen cautery punches and two suprapubics. Six were for valves, 1 for valve and bar, 7 for contractures of the vesical neck and 2 for lobules. The child's punch was used in 9 instances and the baby punch in 5.

Preliminary treatment. All of these little patients, who carried residual urine and who showed evidence of urosepsis, were treated in a manner similar to the prostatic by preliminary indwelling catheter drainage, copious flushings and urinary antiseptics, oftentimes by the administration of subcutaneous saline and intravenous glucose and occasionally by transfusions until their condition appeared sufficiently satisfactory for any type of surgical operation. This type of preliminary treatment is just as important in children as it is to the prostatic. The operation is never performed until the nitrogen is normal, the febrile reaction has subsided and the general appearance of the child is good.

Technique of operation. The punch with its obturator is passed into the bladder which has been previously filled with sterile water or boric. In the infants, the baby punch, a No. 14 French size is used and in larger children the child's punch, a No. 18 instrument, is employed. Following the introduction of the instrument, the ob-

turator is removed, the instrument gradually withdrawn until the water ceases to flow. One is then assured that the vesical orifice is within the slot of the instrument. Previous cystoscopic examination has determined the exact nature of the obstruction, and if it is a contracture of the neck, the slot of the instrument is brought out in the midline below. The eye-piece of the instrument is lightly elevated, steadily securing the obstructing orifice within the slot, the tube is evacuated and dried with a cotton pledget, the orifice is visualized by reflected light and the working element carrying the cautery blade is passed through the sheath of the instrument until it engages the obstruction, the heat is then turned on and by a rotary motion the obstructing band is punched out. The instrument is then removed unless further removal is deemed advisable. At times three bites are removed, seldom more. In case more bites are required, the instrument is reinserted into the bladder, water allowed to flow, orifice grasped again lateral to the previous bite at 5 or 7 o'clock on the dial and the procedure repeated.

In cases of valves, which are always lateral, the instrument is inserted in the same manner but the slot of the instrument is pressed toward the side from which the operator expects to remove a central section from the band, the eye-piece of the instrument passing in the opposite direction until one appreciates a hang and the water ceases to flow. The same process of removal is undertaken. Usually in the valve cases only two incisions are necessary, one on each lateral valve.

In none of the patients operated upon by the punch has there been the slightest bleeding. A small indwelling catheter is inserted for 24 hours. There has never been a postoperative hemorrhage and in only one instance was there the slightest febrile reaction. These children have tolerated such operations much better than have the adults. No complications have occurred. The operation is of course delicate and heavy pressure must not be exerted for fear of cutting too deeply. With light cauterization, there is no danger of deep penetration of heat with the creation of slough beyond the field of operation. The high frequency current as a means of resection would be extremely dangerous in tissues so thin and delicate.

The after-care consists in accurate supervision, daily passing the catheter for vesical instillation of some mild germicidal solution and for the determination of the emptying ability of the bladder. If the bladder empties completely, all instrumental manipulation ceases. If some residual remains as a result of edema, catheterization and instillation continue until it entirely disappears. If within 10 days the urinary function is not normal and residual is still present the child is reexamined and another operation performed. This has only been necessary in two instances.

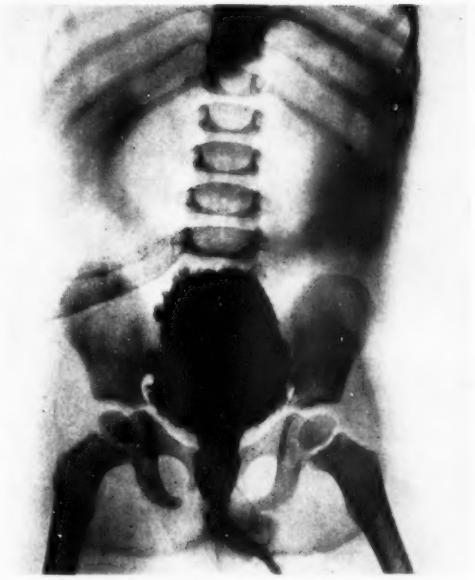

Fig. 1. Contracture of the bladder neck and valves with dilatation of the urethra, marked trabeculation with cellules.

The two suprapubic operations were performed a number of years ago, before the baby punch was perfected and would not have been necessary at the present day. Since these obstructive conditions in children are either from contractures or valves, there should seldom if ever be the necessity for an open operation for their removal.

Results. Thirteen of the operations have given perfect results; 2 decided improvement but not completely satisfactory. The parents refused to allow further surgical procedures. One was not improved. This was a patient with pronounced spina bifida with a very thin delicate valve. The removal of the valve gave no benefit.

The results following the removal of the obstruction through the urethra in children by means of the punch have been the most gratifying I have ever had in surgery. The end-results have been exceedingly satisfactory; invalid children have been restored to excellent health by a simple procedure with practically no complications or untoward effects and with no mortality.

Fig. 2. Contracture of bladder neck. Regurgitation up ureters with marked dilatation and tortuosity relieved after punch operation.

Fig. 3. Contracture of vesical neck, high residual urine, regurgitation, dilatation of ureters, marked infection, and uremia. Complete cure with restoration of function following cautery punch operation.

There have been several cases so striking in the series that they are worthy of special mention.

CASE 1. A boy 9 years of age had had a meningocele removed when a baby. The local result was excellent but he had been incontinent all of his life and had worn a rubber urinal. Numerous urologists whom his family consulted in his behalf expressed the opinion that the bladder incontinence was due entirely to the nerve lesion. When I examined this child he had a typical neurogenic bladder, that is, a markedly relaxed internal sphincter which allowed visibility of the whole posterior urethra. He carried 8 ounces of residual urine. On close cystoscopic study I observed two small valvular folds running from the internal orifice of the bladder out to the region of the verumontanum. These were resected in their central portion by the baby punch. The child immediately began voiding a better stream and within a month had discarded his urinal, his urinary function was perfect and has remained so for the 3 years I have followed him.

CASE 2. A girl of 6 had 300 cubic centimeters residual, marked regurgitation, and tortuosity of the ureters and dilatation of the renal pelves. I have watched the patient for a number of years and have noted the striking observation of the re-coaptation of the uretero-vesical valve. This child at present shows no regurgitation up the ureters after marked distention of the bladder. She had suffered with chronic pyelonephritis since infancy and is now entirely well except for a slight bacteriuria.

CASE 3. Girl of 5 years with 600 cubic centimeters residual, had tremendous dilatation of the ureters and renal pelves and marked uremia. She had suffered with and had been treated for chronic pyelonephritis since infancy. She has been entirely well for 3 years following the removal of but one section of tissue from the midportion of a vesical neck contracture (Fig. 2).

CASE 4. A boy of 4½ years of age, who was observed during the last year, had suffered with pyelitis since infancy and had been treated constantly by qualified pediatricians. He was desperately uremic carrying a nitrogen retention of 90. There was a dirty residual urine of 350 cubic centimeters. He required preliminary catheter drainage for 3 months. Cystoscopic examination showed, with only local anesthesia, a contracture of the vesical neck. A cystogram revealed a tremendous bladder, both ureters regurgitant, and more than an inch in diameter. The renal pelves were tremendous. The roentgenogram of the completely filled bladder, ureters, and kidneys practically covered the entire abdomen. Within 24 hours after the removal of the obstruction by means of the punch, the child voided 8½ ounces whereas he had previously never voided over 2 ounces at a time. Within a month the urine was per-

fectly clear, and the bladder was emptying completely. He has gained 6 pounds in weight and is entirely well (Fig. 3).

CASE 5. A girl, 26 months old, had been a subject of recurrent febrile attacks for many months. Pus and bacilli had been found in the urine constantly, but there were no bladder symptoms. She had been examined elsewhere and a double ureter and renal pelvis was found on the right side with infection in the upper pelvis. Heminephrectomy had been advised. My examination revealed an obstruction at the orifice of the bladder due to valves, retaining 3 ounces of residual urine. The orifice of the ureter, which drained the infected portion of the kidney, was regurgitant. Following the removal of the valvular obstruction at the bladder neck with the baby punch, the residual urine disappeared, and with it the infection in the kidney pelvis.

This case shows the absolute necessity of observing the nature of the vesical orifice, of determining the residual urine, and of making a cystogram.

After the relief of obstruction and free drainage afforded through normal bladder emptying, the ureters will usually empty themselves completely. In some instances repeated ureteral catheterizations are required to applicate the pelves and ureters topically and to hasten resolution. I have never seen a case in which emptying was not sufficient, in spite of the large tortuous ureters, to insure relief of absorption. Periureteritis with fixed angulations seldom occurs in infants and children. With the proper relief of obstruction from below, absorption of periureteral inflammatory reaction will usually result as the infection recedes, and I see no indication for the extensive ureteral plastic operations such as freeing both ureters, straightening out angulations, and resecting several inches of the duct requiring anastomosis. This operation is extensive and serious and misses the point entirely. It is designed to treat the effect and not the cause, and hence should have no place in this class of case.

This series of cases of bladder neck obstruction treated by transurethral removal is, as far as I can determine, the only one so far reported. I urge the profession to suspect such mechanical causes for the majority of persistent or recurrent cases of pyelitis in infants and children and to seek early investigation for such cases so that prompt corrective measures may be applied.

I can sincerely recommend the cautery punch operation for the removal of the obstructions at the bladder neck in infants and children. The procedure is delicate but strikingly simple. It has been entirely free from complications such as hemorrhage and reactions. There has been no mortality and the results have been immediate, durable, and most gratifying. This method of treatment should entirely supplant any major surgical procedure.

INFRA-RED PHOTOGRAPHIC STUDY OF THE CHANGING PATTERN OF THE SUPERFICIAL VEINS IN A CASE OF HUMAN PREGNANCY

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SINCE the advent of infra-red photography, the superficial vascular system in the living is becoming an interesting field of study.

The sole objective of this paper is to present to the clinician an infra-red photographic method for the visualization of the superficial blood vessels in the living. This method may be used in the study of the normal and abnormal superficial blood vessels by any clinician, who has available the ordinary photographic equipment. The only additions necessary are Eastman's infra-red plates type 1R and the infra-red filter.

This method, which has been in use here since 1933, has proved useful in the study of the following clinical conditions: varicose veins, superficial tumors, and thrombosis of superficial and deep vessels with subsequent changes in the superficial collateral circulation. In other words, it is of value in any condition that affects the superficial circulation in which heretofore the opacity of the skin prevented the making of clear photographic records.

PHOTOGRAPHIC MATERIALS AND METHODS

Photographic materials, methods, and various applications of infra-red photography are discussed in previous publications[1].

The infra-red photographs shown in Figures 2 to 8 were made with Eastman infra-red plates type 1R. Any ordinary camera may be used: it is merely necessary to place over the lens a Wratten No. 25 filter and focus the image visually with this filter in place.

The most convenient source of illumination is the incandescent tungsten filament lamp. Other sources are sunlight and arc light. In Figures 1 to 8 two 500 w. tungsten lamps were placed at an angle of about 45 degrees, and about 36 inches away from the patient. It is important at all

[1]Massopust, 1934.

Fig. 1. Ventral aspect of the thorax and abdomen of a 2½ months primipara 22 years of age. Illumination, two 500 watt tungsten lamps. Eastman superspeed film. One second exposure, diaphragm set at focus 22.

Fig. 2. Infra-red photograph of the same case and at the same stage as Figure 1. Illumination, two 500 watt tungsten lamps. Eastman infra-red plates type 1R. Wratten A filter. One second exposure, diaphragm set at focus 22.

Fig. 3. Infra-red photograph of the same case at 3½ months. All of the conditions and factors in the photographic technique are the same as in Figure 2.

Fig. 4. Infra-red photograph of the same case at 5 months. All of the conditions and factors in the photographic technique are the same as in Figure 2.

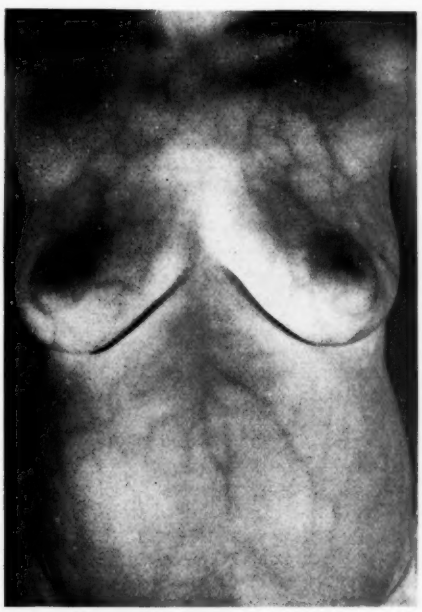

Fig. 5. Infra-red photograph of the same case, 2 days before delivery (same photographic technique).

Fig. 6. Lateral aspect of same stage with all conditions and factors remaining the same as in Figure 5.

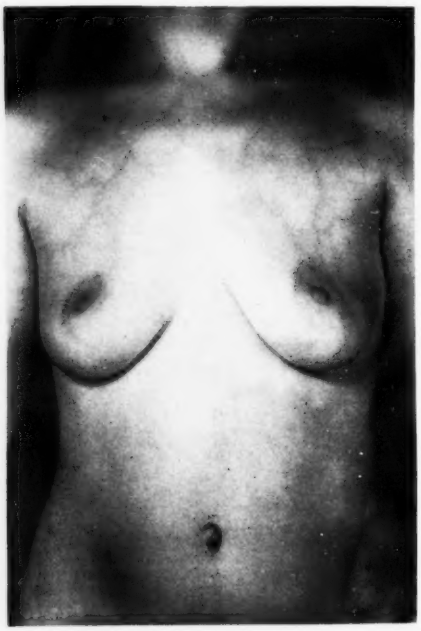

Fig. 7. Infra-red photograph of the same case shown in Figures 1 to 6, 11 months after delivery. The photographic factors and conditions are the same as in Figure 5.

Fig. 8. Infra-red photograph of the lateral aspect of the same stage as in Figure 7 with all conditions and factors remaining the same.

times to strive for a flat illumination of the patient, for in general the gradation of the infra-red plate is so fine that very delicate shades of intensity are clearly rendered. This illumination is sufficient to obtain a properly exposed negative in about 5 seconds with the diaphragm set at focus 22.

Movement and breathing should always be controlled by a method most suitable for the part being photographed. It should be kept in mind also that in infra-red photography profuse growths of hair on the extremities, thorax, and abdomen will obscure practically all of the underlying skin surface. When present, removal of hair will aid in obtaining a clear photograph.

Plates should be handled and developed in total darkness. Many of the older type plate holder slides are somewhat transparent to infra-red rays and hence when used with the infra-red plate will cause fogging. The hard rubber plate holder slides manufactured by the Eastman Kodak Co. bearing five dots on the metal top of the slides are quite safe. Eastman X-ray developer (formula D-19) was used, the average time of development was 3½ minutes with the solution at 65 degrees F. It is advisable to agitate the solution continually to prevent streaking.

The case illustrated in Figures 1 to 6 which was observed for a period of 7 months and photographed at intervals, and which proved to be a normal pregnancy in every respect, demonstrates the gradual change in the photographic pattern of the superficial veins in the breast and abdomen during normal pregnancy. The gradual changes in the conspicuousness of the superficial veins in the breasts indicate that a gradual preparation for lactation is taking place which reaches its maximum directly after delivery when the mammary glands are actively functioning. With further observations and study, this method may reveal the future capacity of the breasts to function adequately in the production of breast milk.

That there is an increase in the size and conspicuousness of the superficial vessels in the breasts and abdomen during pregnancy is an established fact. Infra-red photography, however, has made it possible to record these vascular changes as they occur, thereby furnishing a permanent photographic record for comparison during the progression of the pregnancy. The appearance of the same patient 11 months after delivery is illustrated in Figures 7 and 8 in which

it will be seen that the superficial vessels have again resumed their normal appearance.

CONCLUSIONS

Infra-red photography demonstrates the variable patterns in the superficial vascular system in the living and furnishes a permanent photographic record of any progressive or regressive change in these patterns.

REFERENCES

1. MASSOPUST, L. C. Infra-red clinical photography. Radiography and Clinical Photography, 1934, 10: 2–6.
2. Idem. Infra-red photography in anatomy. Some experimental observations. Anat. Rec., 1934, 61: 71–79.

THE SURGICAL TREATMENT OF ACUTE PANCREATITIS

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A STUDY has been made of the cases of pancreatic disease treated at the Second Surgical Clinic during the past 8 years. During this time 19 cases of pancreatitis were observed, a high number considering the rarity of this disease.

There were 13 women and 6 men—68.4 per cent and 31.6 per cent, respectively. These figures confirm the general experience that pancreatitis is an illness which affects women principally. Schmieden's statistics show 64.9 per cent women and 34.4 per cent men. It is well known that cholelithiasis is a very important factor in the etiology of pancreatitis; if the ratio mentioned is compared with that of our 1200 cases of biliary calculus in which the patients were operated upon during the last 8 years, it is found that the number of women was distinctly greater. Although the number of cholelithiasis cases in our clinic shows a tendency to increase, we were not able to find an increase in the number of pancreatitis cases, as reported by several authors (Lotheissen, Haberer). We believe that single irregularities in percentages are a matter of chance. In 1934, 8 of the 19 cases were observed.

As to age incidence the average age for women was 50 years while that for men was 46 years—the youngest was 29 years, the oldest 70. In the cholelithiasis cases we find that the greater number of patients were of advanced age.

Sixty-five per cent of the patients were fat and corpulent. Schmieden's statistics show the proportion between fat and asthenic persons as 794 to 175. Three patients showed very distinct symptoms of arteriosclerosis. An additional predisposing factor was the presence of biliary calculus; in 13 cases, or 68.4 per cent, stones could be demonstrated. Schmieden reports biliary stone occurring in 69.8 to 81 per cent. Reviewing the operation and autopsy protocols, we found that in 2 cases stones could be traced in the dilated choledochus and in 2 others only a very widened choledochus was found. In each of the cases it was possible that a calculus temporarily obstructed the papilla, that is, that stasis of bile was produced. This seemed possible since the anamnestic data noted the presence of icterus. The activation of the ferments in the pancreatic duct can be explained in this way. We should not fail to mention that according to the results of Hofhauser in our clinic the common action of bile and pancreatic secretion does not produce necrosis in all cases. Hofhauser used dogs in his experiments, implanting the duct of the functioning pancreas into the fundus of the gall bladder; in spite of this he observed no signs of necrosis. It would seem to be true that stasis of bile does play rather an important rôle among the not well understood factors which cause acute pancreatitis. In one of our cases both the common bile duct and the duct of Wirsung terminated commonly in the papilla, and in addition the gall bladder was full of stones, so that there was a possibility that either bile or duodenal juice penetrated into the pancreatic duct. This finding occurs, according to the data of the literature, in 20 per cent of the cases. We observed in 2 cases a wide duct of Wirsung and in 1 of them the duct was of a greenish color due to the bile. In the cases enumerated, besides the biliary calculus, there was the anatomical possibility, that the changes due to the two secretions into the duct predisposed to a pancreatic necrosis.

In 3 cases no pathological change could be found either in the biliary vessels or in the gall bladder itself. It is a fact that cholelithiasis cannot always be found in all cases—according to Mayo it was noted in only 81 per cent and to Riese in 60 per cent—and it is possible that there is a stasis of bile without anatomical changes

which is based on the dyskinesia of biliary vessels (Stocker, Walzel, Lang). If in addition to the pathogenetic factors mentioned—disturbance of the blood supply, biliary stasis, penetration of the bile and duodenal juice into the pancreatic duct—infections of the hepatic system are considered, then nearly all conditions which may cause acute pancreatic necrosis—have been given. Infection takes place upward along the lumen or through the wall of the pancreatic duct, or downward by means of the lymphatic system. Infection was probably present in 4 of our cases.

In 3 cases neither the operation nor the autopsy revealed any special explanation for the actual state of the gall bladder, especially regarding the biliary vessels.

It is a well known fact that the duodenum, the biliary vessels, and the pancreatic system are very closely connected with each other; therefore any changes in one produce a very distinct effect upon the others. For this reason the primary focus of a single disease is still open to much discussion and the prompt localization of the point of origin is indeed a difficult problem. It can reasonably be stated that in diseases and functional disturbances of the hepatic system, the pancreas plays the rôle rather of the victim—pancreatitis—than of an intermediator.

Two cases of pancreatitis are not reported with the 19 others because of their special pathogenesis. In one, a tumor the size of an almond was extirpated from the papilla of Vater through the transduodenal route—carcinoma adenoides. The patient died after the operation from necrosis of the pancreas. Although the autopsy revealed the conditions causing pancreatitis—a wide choledochus, a wide duct of Wirsung, marked biliary stasis the result of obstruction produced by the tumor—it is true that the extensive necrosis might have been caused by trauma incident to the operation. In the second case, a deep callous ulcer was extirpated according to the Billroth II method, with partial resection of the head of the pancreas. A circumscribed necrosis of the head of the pancreas followed operation.

These so called postoperative pancreatitis cases—Schmieden collected 145 of them—affirm the experience that from the operative viewpoint the pancreas may be considered a very sensitive organ. Finsterer performed partial resection of the pancreas in 71 cases of carcinoma of the stomach: 23 of the patients died following the operation and in 9 he ascribed the lethal outcome to injury to the pancreas.

Regarding the diagnosis of acute pancreatitis, it can be stated that there are no symptoms absolutely peculiar to this disease. We recommend the acceptance of the advice of Koerte that disease of the pancreas should not be overlooked in any case of serious abdominal disease. Very often the disease cannot be diagnosed with its classical symptomatology, still it can be differentiated from other acute diseases which resemble pancreatitis and the treatment of which is nowadays generally known and accepted. As to the value of chemical tests to determine pancreatic function, opinions differ greatly—Guleke, Unger, Heuss, Roepke, Redwitz, Reuter, Koch, Bernhard, Mackenzie, etc. It is true that in addition to the clinical symptoms careful examination of pancreatic function is of great value. Determinations should be made of the diastase content of the blood, urine, and duodenal juice, the lipase content of the blood, and the sugar tolerance. In some cases, however, the patient's pulse is barely perceptible and the surgeon has no opportunity to make all these tests, even though he has at his disposal a perfectly equipped laboratory and the necessary assistants. If only one of the mentioned tests is selected to be done and the test is one which is quickly done and which does not strongly affect the patient, it should be stated that no one of them has pathognostic value; on the basis of experiments which were performed in our clinic by Király, even a strongly positive Wohlgemuth test of the urine has no practical value.

We value the leucocyte count highly. In most cases the leucocytes are distinctly increased in number—12,000 to 20,000. The count must be made quite frequently, especially in the cases, when delay is necessary. In our experience the sudden increase in leucocytes up to hyperleucocytosis—32,000 to 35,000—indicates a bad prognosis; on the other hand diminution indicates rather that the process is calming down.

In our cases the urine never contained sugar. We did find albumin frequently, several times bilirubin, and urobilinogen. The prognosis is very bad if the urine is concentrated and the quantity diminishes so that finally there is total anuria. In one of our unfavorable cases which progressed rapidly and in which a diagnosis of uremia was made, we found at autopsy among other changes parenchymatous degeneration of both kidneys caused probably by toxic action, and a widespread fat necrosis of the fatty capsule of the left kidney. Sohn has published a similar case.

X-ray examination is important, first of all from the standpoint of differential diagnosis. Although we were never able to diagnose acute pancreatitis with the X-ray, nevertheless, many diseases could be ruled out by means of it and this was of value,

especially from the standpoint of treatment. X-ray examination was found of great value in detecting the results of acute pancreatitis; for instance, in 1 case we diagnosed a pseudocyst of the pancreas, in another a retroperitoneal cyst.

Summarizing the results, it can be stated that of 19 cases only 4 were definitely recognized as pancreatitis and 2 were diagnosed as probable pancreatitis. Six of our patients were in such poor condition that we decided against even exploratory laparotomy, although very serious abdominal complaints were noted.

Acute pancreatitis is certainly a very serious illness. Of our 19 patients 11 died, making the mortality 58 per cent. Two patients were not operated upon because of their serious condition; both died very early. The mortality therefore of the 17 patients operated upon is 53 per cent.

From the standpoint of clinical symptoms and the operative and autopsy findings, our cases varied greatly; therefore, it seems advisable to divide the cases into three groups on the basis of their clinical symptoms, that is according to the pathologico-anatomical changes.

I. Very serious cases with extremely sudden onset, rapid progress, and usually an unfavorable outcome. In these cases the autopsy shows widespread fat and pancreatic necrosis, colliquation, abscess, hemorrhage.

II. Semiserious cases with acute onset and a tendency to subside. In these the autopsy reveals edema with less extensive fat necrosis; smaller sequestration, circumscribed abscess, and in farther advanced cases pseudocysts.

III. Mild cases with acute onset which ordinarily subsides. Autopsy reveals edema with fat necrosis.

It should be mentioned that we do not regard isolated edema without fat necrosis as pancreatitis; we consider it just the preliminary stage. Fat necrosis was observed in every case.

In the first group there were 6 cases; in the second 9; in the third 2 cases; a total of 17 cases.

Seventeen patients were operated upon, 9 immediately, 8 others after an interval of 20 days and only after the clinical and chemical examinations were made. Of the 9 patients immediately operated upon, 6 were in group I and 3 in group II.

In general, those in very serious condition and some in less serious condition were operated upon immediately; in 2 cases the diagnosis of pancreatitis was definite, in 1 case it was only probable. The 6 others were operated upon for peritonitis and ileus.

After a period of waiting 8 patients were operated upon, 6 cases in group II and 2 cases in group III. Thus in some of the less serious cases and in some of the mild cases operation was delayed so that the acute stage of pancreatitis was observed in the clinic. After administering drugs to raise the blood pressure and infusion, all the patients recovered from shock and collapse, even the patient who died later and who had been operated upon 8 days after the onset to drain an abscess. In 2 serious cases pancreatitis had been diagnosed when the patients were admitted to the clinic. In 1 a cyst formed during the interval of waiting and was subsequently operated upon. In the other patient the symptoms of biliary calculus were clinically observed and at operation an inflamed gall bladder without stones, edema, and fat necrosis was noted. In 1 case the diagnosis was probable pancreatitis, and when the gall bladder and stones were removed, a circumscribed fat necrosis and a marked edema were observed around the pancreas. In 2 cases pancreatic cysts were operated upon, although they could not be diagnosed when the patients were admitted to the clinic. One of our patients was in very bad condition and had stenosis of the pylorus as revealed by X-ray examination. At operation marked edema, fat necrosis, and a distinct constriction of the pylorus were noted. In 2 mild cases our diagnosis was extragastric tumor, cholelithiasis; in both of them subsiding pancreatitis could be observed.

Therapeutic results after immediate operation:

	Cases	Deaths	Recoveries	Mortality per cent
Group I	6	6	0	100
Group II	3	2	1	66

Therapeutic results of the operation after delayed treatment:

	Cases	Deaths	Recoveries	Mortality per cent
Group II	6	1	5	17
Group III	2	0	2	0

We are quite aware of the fact that the number of our cases is small. It must be admitted, however, that the results after immediate and delayed operation show a remarkable difference.

In group I, patients operated upon immediately did not survive the trauma of operation. It should be stated that many types of operations and kinds of anesthesia predispose in certain patients to shock and collapse and we do believe that it should not be stated that operation cures the collapse or that the presence of shock does not

contra-indicate immediate operation. It is very important in acute pancreatitis that the patient come safely through the period of collapse or shock to secure the best operative result. For this purpose we have numerous means at our disposal which act rapidly and which can be used successfully. All our patients were thus treated before operation.

In group II only 1 patient survived, a mortality of 66 per cent.

Our statistics show that immediate operation was done in the serious and less serious but not moribund cases. But since all the patients except 1 died, it can be stated that operation was of no special advantage. Although pancreatitis is quite a serious illness, it may be supposed that by delaying operation spontaneous recovery may take place and thus an improvement will be brought about in our statistics. Our immediate operative procedures were based upon the uncertainty of the diagnosis.

In the less serious cases operated upon after delay—group II—the mortality was 17 per cent; in contrast with the mortality of 66 per cent in the immediate operation group. This striking difference and the zero mortality in the mild cases belonging to group III obviously prove that delayed operation is by all means advisable and correct. If after the acute stage an abscess or a cyst is formed, there is still plenty of time to operate upon the well prepared patient, who will be in much better condition after treatment for the initial shock. The patient who died after the abscess was opened demonstrates that pancreatitis is a very serious illness and that during operation isolation of the free abdominal cavity does not always succeed.

We mention briefly that in 3 cases of the emergency operation group, the gall bladder was removed, in the other cases only the usual opening was made with tamponade and drainage. In all patients operated upon after waiting, cholecystectomy was done, that is, the pseudocyst was opened —in 1 case an abscess of the pancreas. The pancreas itself was never operated upon.

In recent years there have developed two different viewpoints regarding the treatment of acute pancreatitis. The advocates of immediate operation—Guleke, Schmieden, Sebening Arnsperger, Koenig, Roepke, Bruenning, Doberauer, Kappis, Martens, Roseno, Brocq, and the French authors —are opposed by those who favor the expectant treatment—Nordmann, Walzel, Pólya, Mikkelsen, Reschke, Fischer, and an ever increasing number American surgeons. While the number of cases and observations of the latter group is small the results have been unexpectedly good, and we believe that eventually the delayed surgical treatment will be generally accepted.

Detailed statistics which show the result of immediate operation are available (Guleke, Schmieden, Brocq). We concur with Walzel that in acute pancreatic disease the pathologico-anatomical changes are very variable; further that the patient's reactions, both as to the disease and to immediate operation, are so different that the conclusions drawn may be wrong and the interpretation of the results of problematic value—in many cases operation is performed without a detailed examination, preparation of the patient, and a correct diagnosis.

The fact that contrary opinions have arisen can be explained by the fact that the operative results are very bad; we believe that early operative treatment did not yield improved results, as is shown by both the earlier and more recent statistics. In Koerte's cases, 1911, the mortality was 60 per cent, while it diminished to 52.2 per cent in the cases of Guleke, 1924, and to 51.2 per cent for those of Schmieden, 1927. From this standpoint it is especially interesting to study the results of the operative procedure of the French surgeons described in the collected works of Brocq. The death of 78 patients with acute hemorrhagic pancreatitis operated upon before 1910 means a mortality of 67.9 per cent, while in 160 cases after 1910, the mortality was 58.7 per cent. Brocq ascribes this "considerable" drop of 9 per cent to the fact that the procedure included not only operation upon the pancreas, but upon the biliary tract—excision with drainage of the choledochus, etc. It may be stated from both the earlier and later statistics that in this sort of work an error of 8 to 10 per cent may easily arise; therefore no reliable conclusions can be drawn. Also it should be stated that since 1910 improvements have been made in the preliminary measures, in the anesthesia, and in asepsis, all of which tend to produce better operative results. This fact is not quite clearly brought out in the statistics. If immediate operation is really the method of choice in the treatment of pancreatitis, there will be improvement in the late end-results, as is so easily seen when early operation is done in the case of peptic ulcer when it perforates into the free abdominal cavity.

The fact that the majority of patients not operated upon, that is, 95 per cent, die does not support in any way the theory that immediate operation is the correct procedure; in our own clinic 2 moribund patients not operated upon died. We believe that some patients not operated upon

die simply because pancreatitis is a serious illness and that no sort of immediate operation could have saved them. We believe that this should be emphasized, for we fail to find in the statistics reasons for the advocates of immediate operation not performing operation in the non-operated upon cases. We are quite sure that the statistics which show a high mortality percentage include a great many moribund patients.

Experience shows that spontaneous recovery at times occurs in cases of pancreatitis. When performing laparotomies, especially in cases after cholecystectomy, we often have found encapsulated areas of fat necrosis on the omentum, the mesentery, and around the pancreas, traces of previous pancreatitis affections. Otherwise the course of the disease is very variable; in clinically helpless cases the patients often make great progress. We observed this fact in the majority of our patients who were operated upon after due observation. If the operation is done immediately it is impossible for such improvement to occur and the surgeon then is inclined to consider the favorable outcome in the mild case as due to the operation.

The statistics of Brocq show how the results of treatment of pancreatitis vary even if operation is performed. In his 50 cases with operation and simple drainage before 1910 the mortality percentage was 58, while in the 112 cases with drainage after 1910 the percentage mortality was 65. This percentage is no doubt distinctly better than that for the cases without operation—the latter show a mortality percentage of 95. However, the favorable results cannot be attributed to the operation alone because it is a generally accepted fact that exploratory laparotomy with drainage is of practically no therapeutic importance (Hahn). We believe that in Brocq's cases only the patients fit for the operation, not moribund patients, were considered, that the minor operative procedure he used did not affect the possibility of spontaneous recovery.

According to Schmieden the result of operation depends on the degree of pathological change in the pancreas. His statistics can be appreciated especially by the surgeons who advocate waiting but the figures are of less interest to the surgeon who favors immediate operation. According to Schmieden the mortality is 23 per cent when operation is done while the pancreatitis is in the edema stage and no fat necrosis is yet present. The edema is considered by many authors to be the initial stage of the pancreatitis; fat necrosis can be seen after 16 hours. We believe that isolated edema does not always indicate the presence of pancreatitis; very frequently in cases of severe gastritis or cholecystitis edema is noted as a secondary change. Therefore, we believe that in patients who were operated upon in this stage and who recovered—77 per cent—no pancreatitis would have developed and that the high mortality percentage is due rather to the operation itself and to the injury thus produced upon the pancreas. In the initial stage of pancreatitis certain symptoms are inevitable: necrosis or hemorrhage, or both together (Walzel). The mortality rate of immediate operation in this stage is 60 per cent; this percentage is only a little better than that for the cases which show the severest changes, necrosis and liquefaction—68 per cent. The latter mortality rate demonstrates the uselessness of operation.

After observation we operated upon only a few cases in the stage of edema and the mortality was zero. Likewise in the less serious cases of somewhat advanced stage the mortality was only 17 per cent. If statistics could be made in a large series of cases in a similar stage, it would be of great help in determining the value of treatment when operation is not done immediately. In the few cases recorded in the literature the results are quite similar to those of our clinic.

TECHNIQUE

In acute pancreatitis the operation consists of the following steps: opening, tamponade, and drainage. The same technique is adopted if the disease is either of infectious or autodigestive origin. Although the technique of operation is based upon the rules for septic cases, it is used in case of fermentative injury too. We believe that this accounts for many of the unsuccessful operations. Besides the operation upon the pancreas, auxiliary operations are performed on the biliary tract. The aim of the latter is to relieve the pancreas, to drain the choledochus, and to use other means in an effort to check the flow of bile. All these proceedings, however, do not materially alter the end-results.

Although we realize that a series of 19 cases is a small number on which to make definite conclusions, we do think that the results of expectant method as practiced in our clinic are worthy of publication.

SUMMARY

We try to overcome both shock and collapse by means of normal salt infusion, and intravenous glucose injection, and by administering camphor, caffein, cardiazol, sympathol.

We try to confirm our diagnosis by means of X-ray examination, by determination of the

leucocyte count, by the Wohlgemuth test of the urine, and by an exact clinical study.

If the cause of the serious abdominal symptoms cannot be detected, or it is not possible to differentiate the conditions from other diseases which would necessitate immediate operation after having carried out the preliminary measures just mentioned, we perform, using local anesthesia, an exploratory laparotomy, the incision lying along the anterior iliac spine; the Sonnenburg line. This minor procedure is quite sufficient to enlighten us as to the point of origin of the disease. If we find that the condition is not the result of perforation of the stomach, duodenum, intestine, appendix, gall bladder—if it is not the result of ileus or some acute gynecological change, we search no further. If we find a pancreatitis associated with severe hemorrhage even though we are quite conscious of the fact that, in most cases, operation is nearly always hopeless, a general anesthetic is administered and an attempt is made to stop the hemorrhage.

If acute pancreatitis has been diagnosed, or if the condition has been differentiated from other diseases which necessitate immediate intervention, the patient is kept under observation. The blood count is made often and urotropine is administered in large doses. If, during the clinical course, anemic symptoms arise; further, if suppuration, that is, an abscess or a cyst forms, surgical intervention is immediately carried out. If the condition is inclined to subside, the patients are carefully examined after 20 to 25 days. In this interval it can be definitely determined as to whether the biliary system is affected. In most of the cases cholecystectomy is performed. If there is a calculus in the choledochus, it is drained out. The gall bladder without stones, but usually inflamed, is routinely extirpated. This operation is of prophylactic importance too, because in our experience we have found that acute pancreatitis does not develop after the gall bladder is removed except in cases of postoperative pancreatitis from injury. If the state of the patient becomes worse, in most cases a fulminating pancreatitis is present; and the disease progresses quickly to fatal termination before operative procedure can be successfully performed.

According to the principles described we expect a future improvement in our statistics.

Of the 8 patients who survived the acute illness 6 afterward were controlled and examined in our clinic. The examination has been performed 6 months and 1 year after the operation; in 1 case even after 5 years. We place special emphasis on this examination, because it is a fact that after acute inflammation, that is after the fermentative injury, disturbances in internal secretion may arise in the pancreas. One patient of Koerte died in diabetic coma 8 years after the operation. Schmieden states that in 18 cases diabetes subsequently developed and that 3 patients died in diabetic coma.

In all of our patients—5 semi-serious and 1 mild—the pancreatic function has been fully examined. The external secretion of the pancreas was investigated by determining the diastase in the blood, the urine, and the duodenal juice and by examination of feces. The internal secretion of the pancreas was investigated by performing a sugar tolerance test.

In our experiments upon the external secretion we found that the diastase content of blood and urine varied within normal limits. In 2 cases we found a higher concentration in the duodenal juice, above 1000, while in other cases nothing of this sort could be registered. The macroscopical and microscopical examinations of the feces, as well as digestion tests, showed no pathological changes. It may be concluded, therefore, that in our cases the external secretion of the pancreas was not permanently disturbed by the acute illness.

The result of the sugar tolerance determinations which indicate the function of the internal secretion, are summarized in Figure 1.

It is quite evident that the blood sugar concentration differs from the normal by elevation to higher values during the first 30 minutes, above 180 milligrams per cent. The curves *6*, *5*, *3* rise even to 200 to 210 milligrams per cent. After 1 hour the curve falls, but it does not reach the low concentration of the control patient. The concentration is higher than 120 milligrams per cent, and after 1½ hours, when the blood sugar of the control patient is quite normal, 100 milligrams per cent, the sugar concentration of the examined persons is still higher. The greatest differences are shown by the curve *6*. The curves *1*, *2*, *4* do not differ much from the normal during the first 30 minutes, but they attain their deepest point later. It was only in the presence of the three highest curves that we found glycosuria during the experiments, and this ceased after 2 hours.

It was our aim to discover a parallel relation between the changes in the blood sugar curve and the gravity of the acute pancreatitis. We found that the most intense change was in the patient who had the mildest case of pancreatitis. This is quite similar to the findings of Tammann, who believes that the disturbances of internal secretion are not in direct ratio with the gravity of the changes found at operation and with the

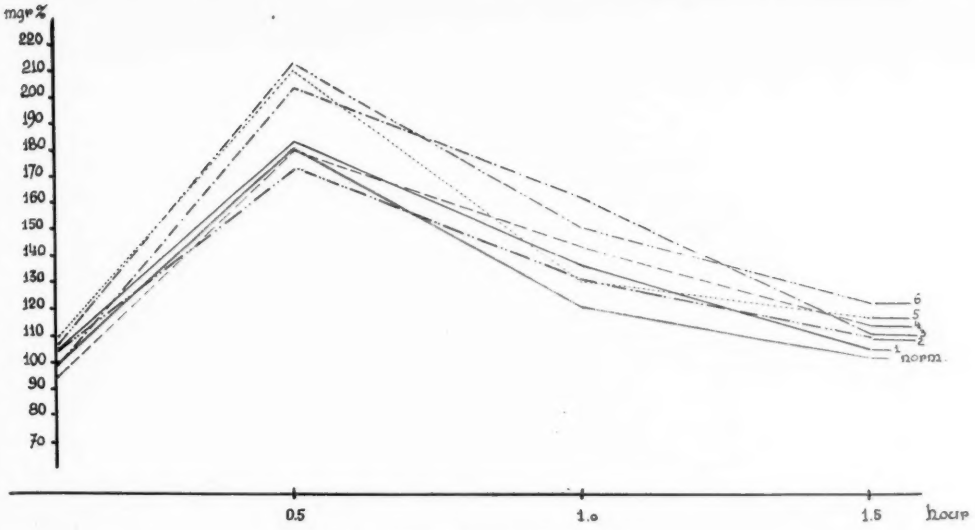

Fig. 1. Sugar tolerance determinations.

length of time which has passed since operation. We did note definitely a certain change in the pancreatic function—internal secretion—which causes us to keep track of our patients. However, the absolute lack of any sort of complaint confirms our belief that after the relief of the acute illness restoration not only macroscopically and microscopically is secured, but even functionally an approximate *restitutio ad integrum* can be shown and only very seldom do late complications, for instance pancreatic diabetes, endanger the patient's life.

GASTROJEJUNOSTOMY PRE-OPERATIVE DECOMPRESSION

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GASTROJEJUNOSTOMY is employed most commonly for the relief of organic obstruction at the pylorus. If the obstruction is one that develops slowly, it often leads to an increase in "size" and "capacity" of the stomach. The stomach walls become thickened in the more muscular portions and dilated in the less muscular portions. Associated with this hypertrophy and dilatation there is usually some edema. Drainage of the stomach by gastrojejunostomy or continuous aspiration is followed by a decrease in length of the muscle fibers of the stomach. This results in a diminution in "size" and "capacity" of the stomach. Associated with this there results an improvement of the circulation in the blood vessels and the lymphatics and a disappearance of the static edema from the walls of the viscus.

This decrease in length of the smooth muscle fibers is generally referred to as an increase in "tone." Yet the intravisceral tension may be the same and the contractile power of the muscle fibers is present regardless of whether the fibers are long or short. This is evidenced by the peristaltic waves which course across the dilated stomach. This relatively fixed condition which smooth muscle manifests at different lengths without a change in intravisceral tension and in which relatively fixed condition the muscle can contract and relax rhythmically has been termed "metrostasis." Dr. A. C. Ivy, who coined the term and defined it, cites the urinary bladder as a classical example. If this viscus is distended within reasonable limits and then emptied of one-half of its contents, the intravesical pressure will be approximately the same as when it was distended with twice as much fluid. This shows that the fibers manifest the same tension at the different lengths, the term "tone" not being strictly applicable, for a change in tone connotes a change in tension.

In the case of the dilated stomach, it can and usually does contract efficiently but the obstruction renders the contractions useless. Relief from the effects of the obstruction by the formation of a new outlet permits the elongated fibers to shorten in length. This results in a reduction in size of the newly formed gastrojejunostomy stoma which was made for the purpose of draining the dilated stomach.

In a previous paper we pointed out the importance of the proper size, location, and direction of the artificial stoma in gastrojejunostomy. It is obvious in the light of our present knowledge that an operation on a dilated stomach presents many obstacles and is less likely to succeed than a similar operation on a stomach properly prepared. We believe that too little emphasis has been placed on the value of thorough pre-operative care in patients whose pyloric orifices have become gradually occluded. The walls of such dilated stomachs are often thickened and edematous. Suturing of these walls is difficult and treacherous. The contour of the viscus and the topographical relations make it difficult, if not impossible, to design an operation that will efficiently serve its purpose in the distended stomach and will continue to serve just as efficiently in the stomach whose "size," "capacity," and contour is changed following drainage.

We have adopted a method of preparation in patients with pyloric obstruction which has given us good results, and we wish to present the details of management in the hope that those who have not made use of a similar method may use or modify the present method to suit their requirements.

METHOD EMPLOYED FOR DECOMPRESSION

At the outset the stomach is evacuated of its gross contents by a stomach pump. Thus undigested food particles which may interfere with suction are removed early. A method of continuous aspiration is then instituted. It is a combination of the methods suggested by Wangensteen, Bartlett, Babcock, Pratt, and Peluse. We are convinced of its efficiency when properly selected cases are treated.

In a recent paper Bartlett uses the term "pyloric balance" to signify the ability of the stomach to empty its contents into the duodenum. He suggests that the term "negative pyloric balance" be applied when the amount of gastric contents which can be aspirated exceeds the amount which has been given by mouth. The term "positive pyloric balance" is applied when the amount of gastric contents which can be aspirated is less than the amount which has been given by mouth.

In the presence of a negative pyloric balance, when the aspirated material exceeds the amount given by mouth, one may assume for practical purposes that the increment may be the result of

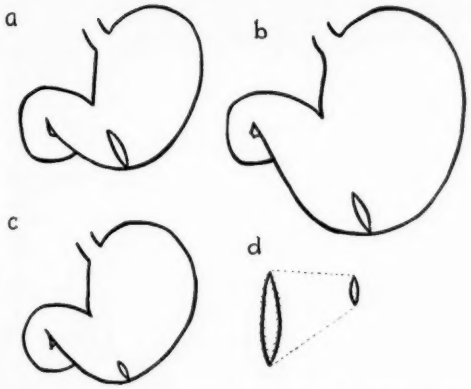

Fig. 1. *a*, The comparative relationship between the stoma and stomach in a viscus of normal size. *b*, The approximate relationship in a dilated stomach. *c*, The relationship between the viscus and the stoma after the dilatation has been relieved by a gastrojejunostomy. *d*, Adjustment of muscle fibers to new length with decrease in size of stoma due to muscle fibers acting in this new and shorter length.

TABLE I.—DATA FROM WHICH FIGURE 3 IS ASSEMBLED

Date 1935	Interval	Amount given by mouth	Amount aspirated	Pyloric balance	Pyloric balance per hour
3–21	1:30 a.m.– 7:00 a.m.	0	75	−75	−12.5
	7:00 a.m.–11:00 a.m.	12	92	−80	−20.
	11:00 a.m.– 3:00 p.m.	24	64	−40	−10.
	3:00 p.m.– 1:30 a.m.	190	310	−120	−12.
3–22	1:30 a.m.– 7:00 a.m.	60	125	−65	−9.5
	7:00 a.m.–12:00 m.	60	90	−30	−6
	12:00 m. – 7:00 p.m.	74	110	−36	−5.1
	7:00 p.m.– 1:30 a.m.	282	325	−43	−6.
3–23	1:30 a.m.–12:30 p.m.	248	300	−52	−4.7
	12:30 p.m.– 9:30 p.m.	154	190	−36	−4.
	9:30 p.m.–10:30 a.m.	306	100	206	+15.
3–24	10:30 a.m.– 7:45 p.m.	294	350	−56	−6.2
3–25	7:45 p.m.– 6:30 a.m.	135	85	+50	+4.5

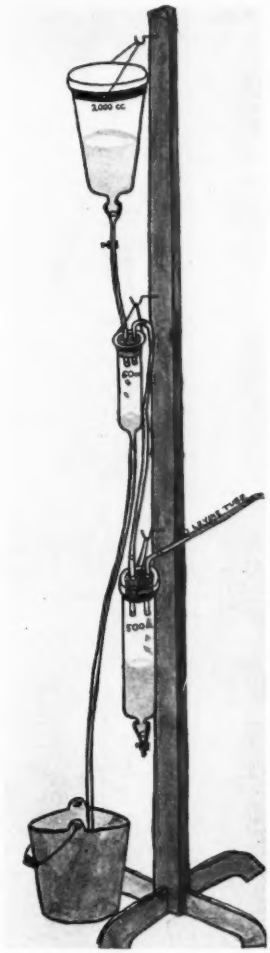

Fig. 2. Diagram of set-up of suction apparatus.

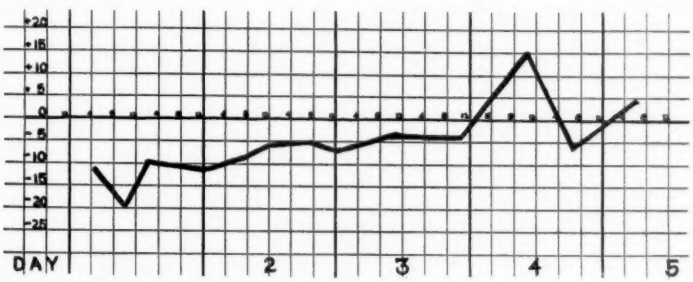

Fig. 3. Pyloric balance chart.

gastric secretion or duodenal reflux. In the presence of a positive pyloric balance, when the aspirated material is less than the amount given by mouth, it may be assumed that the stomach is able to evacuate some of its contents because absorption from the stomach is negligible.

We have adopted the use of these terms and have arranged a chart which assists in keeping an accurate record in graph form of the state of the stomach and its ability to empty itself.

The accompanying chart was made from data compiled from a case of pyloric obstruction on our service. The ordinates represent time intervals. The abscissas represent the aspirated material in cubic centimeters. If a negative pyloric balance is present, it is recorded below the base line. If a positive pyloric balance is present, it is recorded above the base line. Aspirations are computed on an average hourly basis since it may not be necessary or desirable to aspirate more frequently than every 4 to 6 hours.

In cases in which pyloric obstruction results from peptic ulcer, one may be able to establish positive pyloric balance in a considerable number of cases by the use of the method described. Even in pyloric obstruction resulting from malignant lesions, it is not uncommon to secure a positive pyloric balance by the same method. In these cases we have also been impressed by the apparent benefit derived from the administration of 60 to 80 minims of dilute hydrochloric acid three times a day. This is usually given in about 30 cubic centimeters of the juice expressed from raw beef diluted with an equal quantity of water. In all patients with pyloric obstruction careful consideration must be given to the matter of hydration, nutrition, and chemical balance. This is exceedingly important but cannot be considered within the limits of this paper.

It has seemed to us that our operations in cases of pyloric obstruction have been facilitated by adequate preparation and that the postoperative course of patients thus treated amply justifies our recommendation of the plan of pre-operative management which is described.

SUMMARY AND CONCLUSIONS

1. The importance of pre-operative decompression of the stomach is emphasized.
2. A method of decompression is described.
3. A means of determining the appropriate time of operation is brought out (positive pyloric balance).
4. Nutrition, hydration, and chemical balance of the patient must be cared for by appropriate methods.

OBSERVATIONS ON LYMPHOGRANULOMA VENEREUM

Clinical Pathological Study of Sixty Cases, with Observations on the Histopathology of the Frei Test[1]

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In 1786 John Hunter recognized the "climatic bubo" as a clinical entity and as "different from other diseases of the inguinal glands." In 1865 the French clinician Trousseau suggested that the disease in question was of venereal origin. He described a lymph node infection which he had observed particularly among creoles. The disease occurred especially in adolescents, and produced paroxysms of fever and swelling of the inguinal nodes which broke down. Sinuses resulted which took many months to heal.

In 1925 Wilhelm Frei introduced the specific intradermal test which now bears his name. Positive results were found not only in cases of inguinal bubo, but in various pelvic inflammatory conditions as well. Among the latter are included the following: esthiomène, anorectal syphiloma, rodent ulcer of the vulva, pudendal elephantiasis, hyperplastic infiltration of the rectum, and inflammatory stricture of the rectum. Because of the clear cut results with the Frei test, it is now possible to correlate the findings in most of the conditions mentioned and to classify them under a single head of lymphogranuloma venereum.

The infection is usually acquired venereally. The etiological agent is probably a filtrable virus. This virus may be transmitted experimentally to a number of animal species. The onset in humans is characterized by a small initial inoculatory lesion on the genitalia. This is followed by an inflammatory swelling of the regional lymph nodes with involvement of the adjacent connective tissue and lymphatics. In the majority of cases, multiple small foci of necrosis and suppuration occur within the nodes. Constitutional symptoms appear, which include lassitude, fever, sweats, anorexia, loss of weight, transient rash, and arthralgias. The adenopathy in males generally is localized to the inguinal or inguinocruro-iliac group of glands, giving rise to an inguinal bubo. In females the localization of the infection generally takes place chiefly in the intrapelvic glands and the subsequent inflammatory and cicatricial reaction set up in the endopelvic fascia leads to the genito-ano-rectal syndrome.

This report deals with 60 cases presenting histories and clinical findings suggesting lymphogranuloma venereum. The patients presented themselves for observation and treatment at the Mount Sinai Hospital during a period of three years. All of these patients showed a positive Frei intradermal reaction. Negative control cases tested with the same antigen were run simultaneously. Based on clinical and pathological findings, the positive cases were classified into predominantly glandular, rectal, and genital types (Table I).

The lesions among the males are preponderatingly glandular, while among the females they are mainly rectal. There are, however, 8 rectal cases in male patients. It is noteworthy that about half of all the cases were in white males. The hospital population, however, is only 5 per cent negro and 6 per cent Porto Rican. This would account for the high proportion of the white group in this series.

Glandular cases. Inguinal glandular enlargement dominated the clinical picture in 30 cases. There were 29 men and 1 woman. Among these were 19 white men, 4 negroes, 1 negress, and 6 Porto Rican men.

The average age was 29 years, the youngest 16, and the oldest 43.

A history of an initial penile lesion was obtainable in only 12 of this group. The nature of the lesion was described as a papule, vesicle, small laceration about the corona, or a herpetiform lesion on the shaft. Four gave a history of an urethritis which was very probably specific. This is important because it may be confused with a gonorrheal infection. This urethritis differs from that of gonorrhea in that the discharge is loose, shows only leucocytes but no organisms on smear, and disappears within 3 to 4 days, spontaneously.

TABLE I.—CLASSIFICATION

	Glandular		Rectal		Genital		Total
	Male	Female	Male	Female	Male	Female	
White	19	0	6	3	1	0	29
Colored	4	1	0	9	2	0	16
Porto Rican	6	0	2	5	0	2	15
Total	29	1	8	17	3	2	60

[1]From the Laboratories and Clinical Departments of the Mount Sinai Hospital, New York, New York

All of the white male patients in this series gave a history of sexual contact with negresses and some could relate the onset of their disease to such a contact.

The incubation period could not be determined accurately. A time interval of between 2 and 5 days may be considered as likely.

In most of the cases the primary lesion healed spontaneously within 2 weeks after its first appearance. Secondary glandular enlargement occurred from 4 days to 3 weeks after the appearance of the initial lesion. The enlargement was unilateral in 19, bilateral in 11 cases. The 4 cases which presented a urethritis as their initial lesion had bilateral inguinal glandular involvement. The glands broke down and formed pus in 20 of the 30 cases (60 per cent) within 3 weeks after the enlargement was noted. In other words, it takes 6 weeks or less from the onset for the inguinal glands to reach their maximal reaction. By that time they have either broken down or have begun to recede.

The glandular enlargement in all but one of the cases was limited to the inguinal and iliac glands. In this case, which was exceptional, a generalized adenopathy with abscess formation in a submental node, occurred.

The Wassermann reaction was negative in all but 2 cases. One case with a two plus Kahn reaction at the onset became negative after 3 months, without anti-luetic treatment. The other was a known luetic. Bacteriological culture of the pus in all of the cases which had not broken through the skin spontaneously, was sterile. Ziehl-Nielsen stains for tubercle bacilli were also negative.

The relation of the process in the lymphatics to the development of elephantiasis was studied. In 3 cases the inguinal glands were excised bilaterally. In still 1 other extensive suppuration with spontaneous healing occurred. The penile lesion in all these 4 cases healed completely and there was no history of re-infection even so long as 12 years later. None of these 4 developed pudendal lymphedema. In 1 other case bilateral excision of the inguinal glands was followed by marked lymphedema within 6 weeks. The lymphedema, however, was preceded by crops of vesiculopapular penile skin lesions which continued to appear for a number of months. After excision of the inguinal lymph nodes or their destruction by disease, the drainage of lymph is through the scrotum and through the central point of the perineum into the endopelvic glands. This new course seems to form an adequate collateral circulation when no further infection is present on the external genitalia. With a persistent focus of infection the local disease spreads also to the anastomotic lymphatics and an elephantiasis of the penis and scrotum may follow. Similarly, in the female a persistent focus on the external genitalia is likely to produce a vulval elephantiasis.

Biopsy of the inguinal glands in 13 cases showed lesions in 11 which were sufficiently characteristic for histological diagnosis. The duration of the disease at the time of biopsy was usually 3 weeks to 2 months. The 2 cases that presented a picture different from the usual one were of at least 3 months' duration and were both complicated by chronic persistent sinuses and a secondary infection with Staphylococcus aureus. These were the only 2 cases in this group in which a culture of the glands or pus removed was not sterile. This alone may be sufficient to change the pathological picture to one of chronic non-specific adenitis. It is, therefore, justifiable to say that biopsies of lymph nodes not secondarily infected are quite reliable in making the diagnosis.

The problem of treatment of the glandular cases up to the present has essentially been a surgical one. Incision and drainage proved necessary and sufficient in most cases. More radical procedures, such as a complete excision of the inguinal glands, became an optional procedure in a minority of cases. Because of a possible later sequel, such as stricture of the rectum or elephantiasis of the genitalia, after complete excision, it is advisable to resort to more conservative measures. In 2 cases large fluctuant abscesses had formed in the groin. These were treated by aspiration and twelve repeated injections of 0.1 cubic centimeter of Frei antigen. Although small sinuses formed at the site of puncture, both of these cases subsided without any further therapy. Nine cases in all received treatment with Frei antigen in increasing doses. In 5 cases no breaking down occurred, while in 2 cases in which sinuses had formed before the treatment was begun these sinuses closed promptly.

These 9 cases suggest the possible therapeutic benefit of an attempt at desensitization. It is particularly noteworthy that the pain and tenderness of the involved glands disappeared very promptly, even as early as after the second injection. In spite of this, the Frei reaction remained positive even after as many as 60 inoculations over a period of 2 years. This probably indicates the persistence of a focus of low grade infection even when not detectable clinically (9).

Other forms of treatment used in our cases consisted in X-ray therapy, ultraviolet therapy,

foreign protein therapy (typhoid vaccine) and arsphenamine, all without any evidence of success.

It seems advisable, therefore, to treat these patients more conservatively, to provide aspiration where it is indicated, and attempt desensitization. If this should fail, then surgical incision and excision are indicated.

The average time of disability in this series was 2 weeks in the hospital and between 2 and 7 months in the clinic for dressing. All of our group were healed by the end of 7 months.

Rectal cases. Rectal symptoms and signs dominated the clinical picture in 25 cases (Fig. 1). There were 8 men and 17 women. These were distributed as follows: 9 white, 6 being men and 3 women; 9 colored, all being women; and 7 Porto Ricans, 2 being men and 5 women.

The average age of this group is 34 years. This average is higher than that of the glandular cases. This is understandable when one considers the prolonged insidious evolution of the disease in its rectal manifestations. The rectal findings actually represent a secondary phase in the spread of the disease from an original focus on the genitalia. The oldest patient was 58 while the youngest was an 8 year old Porto Rican girl. The latter is the youngest female case on record. She is the child of Porto Rican parents, both of whom have positive Frei tests. The father had inguinal nodes and the mother has a colostomy for stricture (2).

A definite history of an initial lesion was obtainable in only 9 of the 25 cases reported. Of these, 3 were undoubtedly primary lesions in the rectum; 1 in the Porto Rican child of 8 whose symptoms and signs began after injury to the rectal mucosa by an enema tip used by her infected mother; the 2 others were primary lesions in Porto Rican men who volunteered a history of pederasty. However, practically all of the female cases gave a history of some infection of the genital tract, the nature of which could not be attributed to either lues or gonorrhea. The lesions consisted of ulcerations in the vagina, cervix, or about the urethra.

The onset of rectal symptoms occurred as early as 6 weeks or as late as 12 years after a presumed primary infection. The symptoms in order of frequency were blood in the stool, painful defecation, progressive obstipation, growth about the rectum, and pus in the stool.

Enlargement of the inguinal glands was present in 7 of the 25 rectal cases reported. This included only one female. In 6 of the 8 male cases reported there was a definite history of enlargement or suppuration of the inguinal lymph nodes bilaterally.

Fig. 1. A case of lymphogranuloma venereum with rectal stricture showing perianal and pudendal lesions.

These findings are in accord with the accepted view that in males the primary lesion produces an inguinal adenopathy first, no matter what the sequelæ may be. The exception to this rule arises when the rectum itself is the site of the primary lesion, as occurs in pederasty. This proved to be the case in 2 Porto Rican men showing rectal lesions without previous inguinal glandular involvement. They both volunteered a history of rectal intercourse to which time they were able to trace the onset of their symptoms. The Wassermann reaction was negative in all but 1 of this group of 25 rectal cases.

The site of the rectal lesions was limited to the lowest 8 centimeters of the rectum. An abrupt transition from diseased to relatively normal mucosa we found was nearly always demonstrable. The disease presented a varied picture, viz., fistula-in-ano, pelvic cellulitis, acute and chronic proctitis and periproctitis, perianal condylomas, and fibrous stricture of the rectum (Fig. 2).

Biopsy specimens were obtained from the rectal lesions in 9 cases. All of these showed a pathological picture of chronic non-specific inflammation. The inflammatory reaction was more or less severe according to the type of lesion present. There was marked cellular infiltration of the sub-

Fig. 2. Stricture of the rectum due to lymphogranuloma venereum, removed at postmortem.

mucosa predominantly by plasma cells. There were occasional areas of focal necrosis, perivascular plasma cell infiltration, endophlebitis, and focal accumulations of epithelioid cells and giant cells of the Langhans type. This type of pathological picture is helpful only in making a diagnosis by exclusion of other known rectal pathological lesions such as carcinoma, tuberculosis, or lues, with which it may be confused clinically. The non-specific character of the rectal lesion is consistent with the present knowledge of the evolution of the extraglandular lesions. The rectal changes are merely secondary. The specific lesion itself is present, but out of sight in the pelvic glands. These glands show histologically the

Fig. 4. Gross section of resected inguinal lymph nodes. Note the pinhead sized raised nodules present throughout. The focal nodules show central areas which are broken down. Each one corresponds to an epithelioid nodule seen microscopically, i.e., "a stellate abscess."

Fig. 3. A chronic persistent lesion of the penis with lymphedema of 1 year's duration in a case of lymphogranuloma venereum.

identical lesion seen in the inguinal nodes. The inflammatory changes in the rectal wall have been mistaken for syphilis or tuberculosis or nonspecific chronic proctitis. They are all, indeed, chronic granulomatous lesions, but all require confirmatory methods for establishing a specific diagnosis.

The treatment of the rectal cases varied according to the surgical indications, as they presented themselves. Colostomy was necessary in 3 female patients. Two of these cases were re-operated upon through a parasacral incision and the rectum freed from the perirectal fat in an effort to relax the stricture. This proved impossible in one case because of extensive scarring and gave unsatisfactory results in the other. Tartar emetic and fouadin were used in 3 other cases, without any beneficial effect. Bougie and digital dilatation were employed in 4 cases, foreign protein therapy in 1 case, and arsphenamine in another, all without effect upon the local lesion. Repeated injection of Frei antigen 0.1 cubic centimeter every second day, in an effort at desensitization, was used in 4 cases over a period of 2 years. As many as 60 intradermal injections were given. The results at the beginning of the treatment looked encouraging, but after 3 months of treatment the lesions became stationary. Symptomatically these patients feel better, but their local lesions in the rectum show no evidence of regression.

Palliative treatment, such as cotton seed oil instillations, mineral oil by mouth, a low residue diet, may be used first in this type of case. Surgical indications may be taken care of when they arise. Colostomy may be necessary.

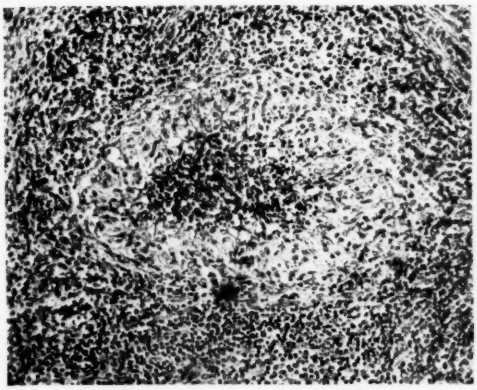

Fig. 5. Epithelioid nodule in a lymph node removed 2 months after the onset of symptoms. Note the invasion of the center by leucocytes, plasma cells, and the absence of extensive necrosis.

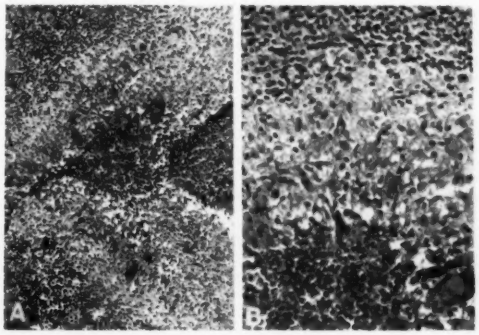

Fig. 6. The periphery of an epithelioid nodule in a lymph node removed 6 months after the onset of symptoms. Note A, left, the giant cells and the invasion of the epithelioid zone by leucocytes and plasma cells; B, right, the palisading of the epithelioid elements.

Attempts at repair of rectovaginal fistulas or of anal fistulas encounter little success. The tissue used in the repair is diseased and does not heal well.

Genital lesions. A group of 5 cases is reported in which the genital lesions persisted beyond the usual 2 weeks period. This feature has not been described previously as such. It forms a definite entity, however, and shows characteristics which identify it with the glandular and rectal forms already described.

There were 3 men and 2 women; 1 white man, 2 colored men, and 2 Porto Rican women.

The average age was 35 years.

The primary lesions in the males began on the corona, glans penis, or the shaft (Fig. 3). These were papular and vesicular in character. In the women the lesions were ulcerations in the vagina at the fourchette and upon the cervix. The disease was progressive from the onset and caused progressive inflammatory erosion of the glans and shaft of the penis, in the male, and of the vagina and cervix in the female. The lesion continued unhealed from 3 months to 12 years.

Glandular enlargement in the inguinal region was present in all of this group. Search for Ducrey bacilli was negative. No gonococci were found.

Biopsy specimens were obtained in 4 of the 5 cases. Pathologically these lesions presented chronic non-specific inflammation, similar to that seen in biopsies of rectal lesions.

The local lesions observed were primary ones which had gone on to further ulceration or perhaps secondary chronic stages of this disease. There is a possibility too that they represent re-infections which made the local lesions assume a different character. The only common histological factor among this group is that the lesions are chronic and inflammatory, otherwise there is nothing specific in the local lesion itself. Here again the biopsy is helpful only in ruling out any other known pathological process. It is not, however, sufficient for specific diagnosis.

The treatment of the genital lesions varied. A good result was obtained in one case with potassium antimony tartrate. In another case, a woman with a pelvic exudate, radiotherapy proved beneficial. In the 3 remaining cases, tartar emetic, arsphenamine, and 1 per cent acriflavine ointment did not affect the local lesion at all.

Again in this group conservative treatment is advisable before radical surgical measures are contemplated.

PATHOLOGY

Lymph nodes. The excised inguinal mass consists of an agglomeration of enlarged glands matted together by an edematous granulation tissue. The capsule appears grayish-red and granular. There are also present punctate raised zones which correspond to areas of softening within the gland substance (Fig. 4). The gland as a whole feels soft and flabby. On section each node reveals many round or irregularly delineated grayish-yellow opaque nodules. These appear like minute abscesses, slightly raised above the surface upon a light gray-red background. The gland may be diffusely speckled with these nodules, but is hardly ever found to be completely necrotic.

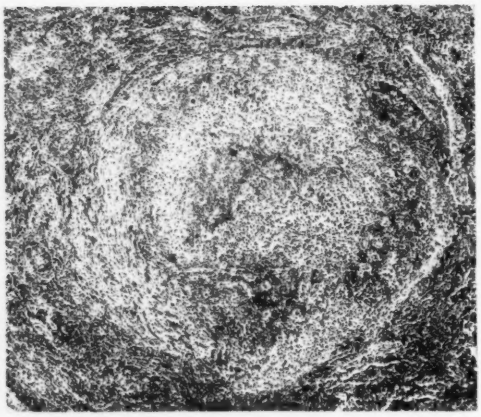

Fig. 7. A single focal nodule removed 3 months after the onset of symptoms. Note the invasion of the center by inflammatory elements, the presence of Gamna bodies, and the giant cells in the periphery.

Histologically the capsule is thickened and fibrous. It shows recent vascularization and infiltration with plasma cells. The septa are similarly affected. The general architecture of the gland is retained to a greater or lesser extent. The glandular parenchyma, however, is altered in the following manner. A general hyperplasia of the lymphatic tissue is present. The lymph follicles are markedly enlarged. The secondary follicles are particularly prominent and show conspicuous reticulum cell proliferation. There is a marked proliferation of the sinus endothelium. The follicles and sinuses are infiltrated by inflammatory elements remarkable for their polymorphism. This is unlike the mononuclear cell reaction in tuberculosis. True caseation and calcification are never found.

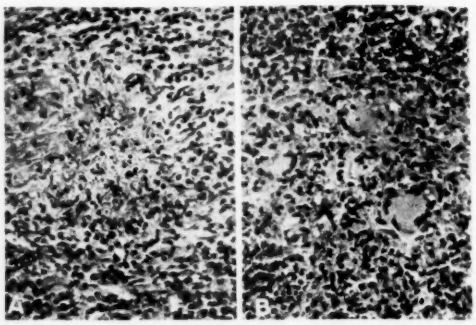

Fig. 8. Punch biopsy of the rectum. Note A, left, submucosal infiltration in a case of stricture, and the epithelioid nodule; B, right, the giant cells of the Langhans type, and the diffuse inflammatory reaction present.

The inflammatory constituents here include plasma cells, neutrophilic and eosinophilic polymorphonuclear leucocytes, and large mononuclear cells from the reticulo-endothelium in addition to multinucleated giant cells.

The grayish-yellow opaque nodules referred to appear microscopically as clusters of cells scattered throughout the gland. These clusters consist of large mononuclear cells with pale nuclei ar-

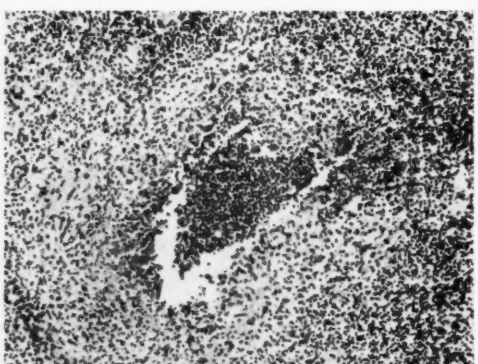

Fig. 9. Iliac lymph node removed from the pelvis at postmortem from a case of lymphogranuloma venereum with rectal stricture.

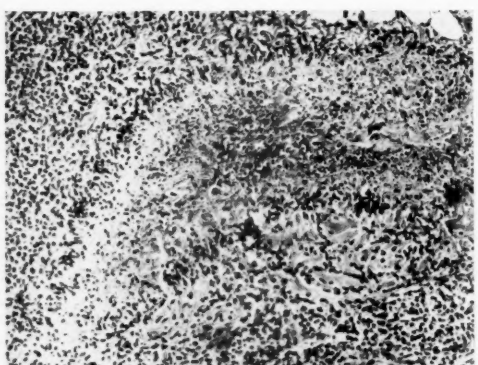

Fig. 10. Section of skin showing the Frei intradermal reaction removed 5 days after injection of the antigen. Note the diffuse inflammatory reaction, the areas of necrosis, and the epithelioid nodule which is identical with the lesion in the lymph nodes.

ranged radially in a palisaded manner (Figs. 5 and 6). Among these cells there occur multinucleated giant cells with peripherally arranged nuclei, not unlike those found in tuberculosis or lues (Fig. 7). On this account these lesions have been referred to by the French as gummas. Their number varies considerably. In some cases they are very numerous and scattered all over the gland; in others, especially the late cases, they are comparatively few. Subsequent changes consist in a process of degeneration whereby the center of the nodule becomes necrotic and manifests a core composed of an amorphous, finely granular or homogeneous material. This core is derived from degenerated cells and is surrounded by a thick layer of epithelioid cells among which there are a good many giant cells. This histological picture has been referred to as a "micro-abscess." It is round, oval or irregularly branching, and very often stellate (Fig. 7). The central portions, containing granular débris, are filled with acidophilic mononuclear macrophages and polymorphonuclear leucocytes. The former cells contain engulfed nuclear fragments. Chromatin-staining bodies, semilunar, dumb-bell-shaped, or pear-shaped, occur free as well as in the monocytes and have been called Gamna bodies, after the observer who first described them. He suggested that they were cell inclusions associated with the virus. It is more likely that they represent nuclear débris.

The fibrillar reticulum, as shown by a silver stain, is well preserved throughout the gland but appears as broken up, thin, irregular shreds within the necrotic center of the nodules described.

This pathological picture in the glands may be taken as characteristic of the disease and reliable for diagnosis.

The earlier stages show more necrosis. The later ones show more fibrosis and chronic adenitis, with a predominance of plasma cell infiltration. In cases which have gone on for more than 5 or 6 months, the specific lesions do not appear clearly. They have probably disappeared for the most part. The specific lesion, however, is still retained in one place or another. This takes on the form of a small epithelioid cell nodule, focal in character, in the cortical zone of the lymph node, and surrounded by a mantle of plasma cells which also invade and distort the epithelioid cell clusters.

Rectal lesions. Among the rectal cases the biopsy specimens in three showed areas of necrosis, distinct perivascular infiltration by plasma cells, occasional giant cells (Fig. 8), and marked vascular changes indicating an obliterating endophlebitis. The histological picture was somewhat suggestive of syphilis. However, the Wassermann test and a therapeutic test were persistently negative. This leads one to view these lesions as suggestive of lymphogranuloma venereum, particularly when supported by the presence of a positive Frei test. The pelvic glands, removed at postmortem, do show lesions identical with those of the inguinal glands (Fig. 9).

Genital lesions. When the genital lesions are reviewed it is again noted that some suggest the picture of syphilis, not unlike the rectal lesions. On excision of an initial lesion, the changes found on histological examination are of the same nature though varying somewhat in degree, whether the lesion is in the form of a little herpetiform ulcer, a papule, or a nodule (5). At the edges of the lesion the epidermis is thickened, the interpapillary prolongations are wider, the papillas are thinned or the interdigitations may have entirely disappeared, the several layers being flattened out by a stratum of infiltration which invades the papillary layer and the superficial part of the dermis. Where there has been a solution of continuity of the surface, the stratum granulosum and the stratum lucidum are destroyed, thus exposing the cavity of the lesion filled with amorphous and cellular débris. The cavity is surrounded not by granulation tissue but by an altered connective tissue filled with lymph cells resembling somewhat a lymph follicle. The Malpighian layer and the prickle cell layer are swollen and edematous, there being both intercellular and intracellular edema of the epidermis leading in places to the formation of a fine spongy vacuolation. Many mitotic figures are visible.

The cellular infiltration is composed of plasma cells, lymphocytes, swollen connective tissue cells, also cells with two or more nuclei. Free nuclei are noted. These look like the Gamna bodies (4). In the subjacent dermis the blood vessels are engorged but though the endothelium is swollen there is little noticeable perivascular infiltration. In other cases the process is more advanced, resembling that in the glands, with the formation of the characteristic micro-abscesses lined by epithelioid cells, marked infiltration with finely granular oxyphile cells and macrophages containing cell inclusions (Gamna bodies).

The Frei test. It is remarkable that the description of the primary lesion corresponds in every way to that of the Frei intradermal reaction. A section of skin showing a positive reaction was removed for histological examination. It shows the characteristic subcutaneous infiltration and necrotic nodule described. It is the formation of this nodule that indicates a positive reaction

(Fig. 10). The surrounding erythema represents a secondary non-specific congestion and tissue reaction about this necrotic nodule. This is readily demonstrable on histologic section.

The primary lesion is thus a papule showing acute inflammation, with necrosis and nodule formation, like the picture of the acute stage seen in the glands. This lesion usually heals rapidly with the formation of a thin scar. If this primary lesion spreads and becomes chronic, the striking pathological picture of the first phase becomes less evident. The lesion now consists of epithelioid nodules, perivascular plasma cell infiltration, endophlebitis, and giant cells. This picture is similar to the rectal lesions. These lesions are also suggestive of syphilis. However, the Wassermann reaction in these cases is negative as are therapeutic tests. Although these chronic lesions do not conform to the histological picture of the acute necrotic nodule, they do suggest a later phase of this disease, similar to the same process seen in the glands and in the rectal wall. These later genital lesions can be traced clinically, as extensions from an acute primary lesion. It is, therefore, reasonable to assume that the histological picture presented is that of lymphogranuloma venereum in a later stage. This is stated in spite of the appearance suggestive of syphilis, and supported by the presence of a positive Frei test.

EXPERIMENTAL TRANSMISSION

Between 1913 and 1922 attempts at transmission of lymphogranuloma venereum to animals were practically uniformly unsuccessful. Since then the transmission has been successful in a number of animal experiments. In order of susceptibility may be mentioned the monkey, the white mouse, the guinea pig, the rabbit, the cat, and the dog. The following series of transfers have been effected: rabbit's brain to rabbit's gland to guinea pig's gland to rabbit's gland to rabbit's brain.

The earlier investigators were content to consider a local glandular enlargement produced by subcutaneous injection as sufficient proof of the transfer of the disease. Later investigators excised the glands and reported changes similar to those obtained in the human cases (6). However, the lack of photomicrographs in their publications makes it difficult to verify the histological picture found in their experiments. At least 10 investigators reported failures with the subcutaneous injection method.

The intracerebral injection of the pus obtained from known cases, however, offered more consistent positive results. A meningo-encephalitis is reported. Focal necrosis with focal accumulation of lymphocytes in addition to perivascular infiltration of the cerebral vessels are given as specific evidences for the successful transfer of the disease. Numerous reports are confirmatory of the findings of a meningo-encephalitis. However, the specificity of such lesions is open to doubt. The injection of any foreign irritant is likely to produce similar changes.

The experiments in themselves are important in that the virus can be preserved in the brain tissue of animals and that an emulsion of brain substance infected by the virus will produce a positive reaction in known cases of lymphogranuloma venereum (8).

Ten guinea pigs were injected in the inguinal region with material obtained from known cases of the disease. The pus was obtained in the operating room under sterile precautions. Four cubic centimeters were used for each guinea pig. All of the guinea pigs developed a glandular enlargement within a period of 10 days. All of the glands that were excised after about 3 weeks showed a lymphoid hyperplasia and nothing more. Bacteriological cultures of these glands were all sterile. In all of the glands which were not excised the process subsided spontaneously. None broke down.

Transfers were attempted in four guinea pigs with both filtrate and macerated glands. These four presented a glandular enlargement which histologically looked like a lymphoid hyperplasia. None of the glands removed showed a picture similar to the human. Frei tests done on these guinea pigs were positive while controls were negative. At postmortem there was no iliac glandular enlargement and no lesions were found in the liver or lungs. This is somewhat contrary to the findings by recent investigators.

CONCLUSION

We are dealing with an infectious disease caused by a filtrable virus and disseminated by way of the lymphatics. It is inflammatory in character and consequently may appear in acute, subacute, or chronic stages. The disease process does not proceed along the lines of any simple well defined pattern. The clinical manifestations are either the local primary lesion, an enlargement of the regional nodes, or the consequent alterations in the neighboring anatomical structures the lymphatic drainage of which is dependent upon the nodes affected. The failure to recognize this multiplicity of syndromes resulted in a confusing terminology or lack of recognition of the common agent.

With the introduction of the Frei test and a more thorough review of the histology of the lesion, all of these syndromes may now be grouped under the one head of lymphogranuloma venereum. The variability of the symptoms depends upon the extent and character of the anatomical involvement. The objective findings, likewise, will be different in each case, varying with the extent of the region involved and the amount of inflammatory reaction taking place.

The histopathological unit of this disease is an inflammatory nodule which undergoes necrosis. The primary lesion demonstrates this nodule in its simplest form. The nodule produced by the Frei intradermal reaction reproduces the lesion identically in every respect. A single lesion may be described as a shell of palisaded layers of epithelioid cells with a central granular core. The contents of this central portion consist of the cellular débris of leucocytes, lymphocytes, and endothelial cells of which this nodule was originally composed. Plasma cells appear in the later stages.

If this necrotic material breaks through its limiting shell and invades the skin, a sinus forms. If the breaking down takes place within the node itself, a coalescent abscess forms. If each individual inflammatory nodule involves the skin and breaks through it, multiple sinuses form. Each of these sinuses drains a separate focus. In the endopelvic fascia, the same holds true. The amount of breaking down determines the extent of the lesion. Small distinct inflammatory foci coalesce to produce larger ulcerations.

The virus is apparently a sluggish one insofar as the disease that it produces may go on in its evolution either to spontaneous healing or to chronicity. Whereas it was previously believed that all cases go on to suppuration, this belief is subject to modification when more cases are reviewed. The fact that many different non-specific methods of treatment effect a cure also speaks well for the possibility of spontaneous cures. However, since this disease is caused by a virus, a biological approach toward therapy seems rational. A method of desensitization seems the desirable form of treatment. Thus far this method has shown much promise.

CASE REPORTS

Glandular Lesions

CASE 1. The following case is fairly typical of the course in a white man showing glandular involvement.

E. L., a 23 year old Italian male laborer, was admitted to the surgical service of Dr. Edwin Beer. He had had coitus with a negress 3 weeks prior to admission. At the time of exposure he noted a small injury at the frenulum. This lesion healed slowly and at the time of admission appeared as a flat subchronic ulceration 5 millimeters in width. Within 1 week after exposure, he noted a progressive enlargement of his inguinal glands on the left side which became painful. He ran a fever to 104 degrees F., had many chills, and lost about 20 pounds in 3 weeks.

The patient presented a large left inguinal abscess and many broken down lymph nodes. In addition, he had a small ulceration, 5 millimeters wide, at the frenulum. He was operated upon and the abscess evacuated. A number of broken down lymph nodes were removed and the patient was treated with 50 per cent glycerine wet dressings. This was done with the knowledge that the virus is unstable in glycerine. This type of dressing gave the patient the greatest relief. The penile lesion healed spontaneously within 3 weeks, without any treatment, leaving a thin scar. The inguinal lesion healed firmly within 2 months and left a deep-pitted scar.

The Wassermann and Kahn reactions were negative. The Frei test was strongly positive. A dark field examination of the exudate from the primary lesion showed no spirochetes. Culture of the pus showed no growth.

Microscopic examination. The lymph node removed showed lesions indicative of lymphogranuloma venereum. A biopsy of the penile lesion showed chronic inflammation. A section of the skin at the point of injection of the Frei material was removed. This presented a necrotic intradermal nodule. The histological changes in the skin nodule were similar to the changes found in the inguinal gland.

Rectal Lesions

The following case illustrates the course of an acute rectal lesion in a white male and the effect of intradermal Frei antigen as a therapeutic agent.

CASE 2. M. E., a 58 year old Turkish Jew, was admitted to the medical service of Dr. B. S. Oppenheimer. The patient had contracted syphilis and gonorrhea 6 years previously. At that time he had received four intravenous and intramuscular injections. Seven months previous to his admission he was operated upon for a fistula-in-ano. He had complained of pain in the rectum and a bloody discharge from the rectum. At the same time he was operated upon for a left inguinal adenitis. During the 4 months previous to his admission he suffered from increasing loss of weight. He had a bloody diarrhea, and much mucus in his stool.

The patient's status was essentially negative except for his local findings. The left inguinal nodes were found to be enlarged and firm. There was a perfectly well healed scar over these nodes. Rectal examination showed a marked periproctitis with a small periproctitic abscess. The rectal lesion conformed to that of a granulomatous proctitis. Sigmoidoscopy showed a sharply demarcated lesion which began at the anus and involved the rectum upward for a distance of 7 centimeters where it stopped abruptly. The mucous membrane presented a cobblestone appearance, was very granular, and bled easily. The perianal (or perirectal) tissues showed marked infiltration. The rectal segment involved felt rigid and fixed to the surrounding endopelvic fascia. There was no stenosis. There were multiple anal fistulas and the rectum contained a raspberry-juice-like secretion. The mucous membrane above the lesion had a normal appearance.

The patient was treated in the wards for a period of 2 months. He was given a course of antiluetic therapy. In addition, he was given azochloramid per rectum. He was also given a course of fouadin (10 doses from 1.5 cubic centi-

meters to 5.0 cubic centimeters intramuscularly). Under this treatment the patient showed no improvement whatsoever and was discharged to the out-patient department. An attempt at desensitization was made in this case, and the patient, up to the present time, has received 60 injections of Frei material intradermally. This method of treatment produced a very satisfactory result. The immediate favorable effect that was noted by the patient was the disappearance of pain. This occurred after 5 injections. After this the diarrhea diminished and the bleeding stopped completely. The anal fistulas appeared cleaner The rectal lesion at proctoscopy showed the mucous membrane to have a healthier appearance and there was no bleeding. The granular areas looked flatter and the secretion in the rectum less. After 3 months of treatment with Frei material the granulomatous lesion showed evidence of slow recession. Symptomatically the patient feels much relieved, but the pathological lesion is far from being cured. There is no evidence, however, of progression toward a stricture. The injection of Frei material produces a positive reaction each time it is used in spite of continued injections.

Laboratory examination of the stool at all times showed blood. The serum agglutinations for dysentery were all negative. The Wassermann and Kahn reactions were negative. The complement fixation for gonorrhea was negative. The blood count was: white blood cells, 9,600; polymorphonuclear leucocytes, 75 per cent; lymphocytes, 23 per cent; mononuclear leucocytes, 2 per cent.

Pathology examination. The specimen consisted of a punch biopsy of rectal tissue, and conformed to the following description: "The epithelium is flattened. The subepithelial tissue is densely infiltrated by lymphocytes, leucocytes, and plasma cells. Fresh and old granulation tissue and one area of necrosis and endophlebitis are also seen. The pathological picture is suggestive of gumma."

Persistent Genital Lesions

The following case illustrates a penile lesion which resisted every form of treatment and went on to involve the glans penis and a good part of the shaft of the penis.

CASE 3. E. H., a 42 year old negro male cook, was admitted to the surgical service of Dr. Edwin Beer in 1933. He gave a history of pulmonary tuberculosis 17 years previously and of a gastric ulcer 4 years previously. In 1913 he required incision and drainage of a right inguinal abscess. In 1917 he had an acute gonorrhea. About 1 month later he had difficulty in voiding. The glans penis became markedly swollen and began to ulcerate. A dorsal slit of the prepuce was performed and the inflammation gradually subsided but there remained a large excavated lesion on the ventral aspect. In 1923 he had a urethral abscess at the base of the shaft of the penis. An incision was required and the patient developed a urethral fistula which remained to the time of his admission. Six months previous to admission there appeared a red inflamed area on the dorsum of the glans penis and the adjacent prepuce. The area enlarged and became painful and ulcerated. Many Wassermann tests were taken and all were reported negative at different institutions. He was treated with salvarsan and mercury, without any favorable effect.

On examination, the glans penis was found markedly deformed. On its ventral aspect there was a large, deep excavation which involved the urethra for a distance of 2 centimeters. The ulcerated area was entirely insensitive. The right aspect of the glans presented an irregular, painful, tender, dirty ulcerated lesion which extended half-way around the glans. The margin of the ulcer was hard and nodular. The adjacent surface of the prepuce was also ulcerated and presented several nodular lesions. The rest of the penis was markedly edematous and tender. At the base of the penis on the left side there was a large opening through which urine passed. Several small lymph nodes were present in the right groin beneath a well healed scar.

The patient was given wet dressings of 50 per cent glycerine, ammoniated mercury ointment, 1 per cent acriflavine ointment, and tartar emetic, without any benefit. He was seen 8 months later. His local lesion had progressed unfavorably with further excavation, ulceration, and swelling. The patient is extremely irregular in his attendance at the clinic and can not be followed up carefully.

The Wassermann and Kahn reactions were negative. The Frei test was positive.

Pathology. A biopsy specimen taken from the penile lesion showed an ulcerative inflamed lesion, nodules with giant cells present, also epithelioid cells, endarteritis and conspicuous endophlebitis. The histological picture suggested gumma.

SUMMARY

1. Sixty cases showing a positive Frei intradermal reaction are reported.

2. The cases fall into three groups according to their presenting symptoms as: (1) lesions involving the inguinal glands, (2) rectal lesions, (3) genital lesions.

3. An attempt is made to correlate the histopathological findings in all three types and put them upon a single basis.

4. The histopathology of the Frei reaction is that of a specific lesion similar to the histopathological unit of the disease as it appears in the glands.

5. The use of injections of Frei antigen as a therapeutic measure is considered advisable.

NOTE.—An additional 30 cases of this disease were observed since this report was submitted. At the instigation of Dr. Robert T. Frank, this disease was made reportable to the Board of Health.

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BIBLIOGRAPHY

1. BERNSTEIN, PHINEAS. Lymphogranuloma venereum. Am. J. Gynec. & Obst., 1935, May, 718.
2. ELITZAK, JACOB, and KORNBLITH, BORRIS A. Lymphogranuloma inguinale. A case with rectal manifestations in a child. Am. J. Dis. Child., 1935, 49: 703–709.
3. FREI, W. New skin reaction in lymphogranuloma inguinale. Klin. Wchnschr., 1925, 4: 2148.
4. GAMNA, C. Sulla linfogranulomatosi inguinale. Richerche cliniche ed etiologiche. Arch. sc. med., 1922, 45; Gior. biol. e med. Sperimentale, 1923, March.
5. GANS, M. Histology, primary lesion and erythema. Bull. Soc. franç. dermat. et syph., 1931, 38: 544; Presse méd., 1931, 39: 529.
6. HELLERSTROEM, S. Experimentelle Untersuchungen ueber lymphogranuloma Inguinale. Dermat. Ztschr. 1931, 61: 395.

7. HUNTER, JOHN. A Treatise on the Venereal Disease, 1786, p.265.
8. LEVADITI, C., RAVAUT, P., SCHOEN, R., and LEVADITI, J. La phenomene des "neuro-infections mortelles auto-sterilisables," etc. Compt. rend. Soc. de biol., 1933, 112: 359.
9. LOEHE, H., and ROSENFELD, H. Intravenous vaccine. Dermat. Ztschr., 1933, 66: 112.
10. REISS, F. Zur Frage der Infectiositaet den sogenannten genito-rectal syndrome als spaetfolge des Lymphogranuloma Inguinale. Klin. Wchnschr., 1932, 49: 2031.
11. STANNUS, H. S. A Sixth Venereal Disease. London, 1933.
12. TROUSSEAU, A. De l'adenie. Clinique medicale de l'Hotel-Dieu-de-Paris. 2d ed., 1865, iii, 581.

ABORTION

A STATISTICAL ANALYSIS OF 2,287 CASES

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THE problem of abortion is an extremely important one, not only to the practicing physician but to the community at large. Spontaneous expulsion of the ovum prior to the twenty-eighth week of gestation is a frequent and often serious complication, occurring, according to Williams, in approximately 1 of every 5 pregnancies. It is probable that this incidence is too low since it does not include many of the very early cases which are recorded merely as "delayed" menstrual periods. It is utterly impossible to arrive at any accurate estimate of the frequency of self-induced and criminal abortion, although many authorities have expressed the opinion that they at least equal the spontaneous type in number and probably exceed it. The mortality resulting from criminal abortion is also a matter of conjecture, but it is agreed to be very high, and Liepmann has stated that it causes approximately 25,000 deaths each year in Germany.

The number of abortions observed on the obstetric service of a university hospital is usually small in proportion to deliveries at or near term. This is due not only to a rather general policy on the part of hospital authorities to discourage this type of admission except in case of emergency, but also because the patients themselves seem to prefer home treatment for this condition. Complicating factors, such as excessive hemorrhage or infection, are usually the direct reason for admission in those cases seen on a clinic service, with an additional small number of abortions which have been induced for therapeutic reasons. From the time of its inception in 1896 to the end of 1934, a total of 2,287 patients with abortion had been observed and treated on the obstetric service of the Johns Hopkins Hospital. It is our purpose in the following paragraphs to offer a brief analysis of this series which comprises 7.60 per cent of the total admissions to the service. For this purpose the case records have been carefully examined in an effort to ascertain points of interest concerning the abortion problem and also to determine the

TABLE I.—TYPE OF ABORTION

	Number	Per cent of total
Spontaneous	763	33.36
Operative	1196	52.30
Missed	41	1.79
Therapeutic	287	12.55
Total	2287	

TABLE II.—RACE AND AGE

	Race		
	White %	Black %	Mean age
Spontaneous	52.69	47.31	25 yrs. 5 mos.
Operative	70.23	29.77	28 yrs. 9 mos.
Missed	65.85	34.15	27 yrs. 6 mos.
Therapeutic	73.17	26.83	30 yrs. 2 mos.
Total excluding therapeutic	63.45	36.55	27 yrs. 5 mos.

TABLE IIA.—PARITY

Parity	Spontaneous—%	Operative—%	Missed %	Therapeutic -%	Total—excluding therapeutic*—%
1	24.77	12.21	21.95	16.38	17.20
2, 3	34.07	25.75	29.26	25.78	29.00
4, 5	17.04	23.49	7.32	20.56	20.70
6, 7	11.53	14.72	26.83	14.63	13.75
8, 9	5.90	10.87	4.88	7.66	8.85
10 and over	6.42	12.04	9.76	13.59	9.85
Unknown	0.26	0.92	0.00	1.39	0.65

(*It will be noted that in this and subsequent tables the totals computed exclude therapeutic abortion. It is believed that by so doing a more accurate picture of abortions in general is attained, since the latter group is a highly selective one, having nothing in common with the others of the series except the premature termination of the pregnancy.)

TABLE III.—SOCIAL STATUS

Social status	Total abortions—%
Single	10.18
Married	87.99
Widowed	0.78
Divorced	1.04

existence of racial differences, if any, between the white and black patients comprising the series.

Table I summarizes the series according to the type of abortion. Since this nomenclature will be used throughout the analysis, these terms may well be defined at this point. Spontaneous abortion is limited to those cases giving no history of criminal attempt and with completion occurring without operative aid. The operative group includes all cases of inevitable or incomplete abortion completed by digital or instrumental curettage, but does not include instances of vaginal hysterotomy. Missed abortion has been diagnosed whenever it seemed clear that a month or more had elapsed between the death of the product of conception and the actual miscarriage. The term therapeutic abortion conforms to the common usage. The fetus in no instance attained a length of 35 centimeters, or a weight exceeding 1500 grams.

The following analyses of the material have been made:

The race, age, and parity are given in Table, II and IIA.

The clinic population from which these cases are drawn is made up about equally of white and black patients. In contrast to this will be seen, from Table II, that almost two-thirds of the patients with abortions were white. Moreover, distinct racial differences were noted according to the type of abortion, as was evidenced by a very slight preponderance of whites over blacks in the spontaneous group (52.69 and 47.31 per cent, respectively), while for the operative group percentages of 70.23 and 29.77, respectively, were found. Whether or not this is a true racial difference is not clear, but it seems probable that a part of the discrepancy at least is to be explained in terms of the greater number of induced abortions on the part of the white patients.

The mean age of the patients in the series was 27 years 5 months, a figure considerably higher than that found for the general clinic population (23 years 10 months). Similarly, only 17.20 per cent of the abortions occurred in primigravidæ, although more than half of the total clinic patients (54.69 per cent) were pregnant for the first time. Interesting differences were found in age and parity according to type of abortion, and the group with spontaneous termination was much younger and contained twice as high a percentage of primiparæ as did the operative group. In general the missed abortion series approximated the operative group in characteristics of race, age, and parity more closely than the spontaneous. Naturally, the patients with therapeutic abortions were largely multiparæ and in the older age groups.

TABLE IV.—PREVIOUS ABORTIONS

Previous abortions	Spontaneous %	Operative %	Missed %	Therapeutic %	Total %
Total patients	32.92	43.40	48.39	35.56	39.08
Total patients excluding primiparæ	42.04	49.19	60.00	41.83	46.62
1 previous abortion	65.84	53.48	46.67	54.69	57.68
2 previous abortions	19.88	21.98	46.67	25.00	22.05
3 previous abortions	6.21	12.09	0.00	9.38	9.58
4 to 5 previous abortions	4.35	8.42	0.00	7.81	6.68
6 and more abortions	3.73	4.03	6.67	3.12	4.01
Average number of abortions per patient with previous abortions	1.72	1.98	2.07	1.86	1.89

Table III indicates the social status of the patients in the series, although it is not our intention to suggest that the figures are characteristic in this respect for abortions in general. It is interesting to note that the incidence of unmarried patients is twice as high (21.80 per cent) in the general clinic population as in this series, a figure to be explained in terms of the large number of colored women cared for by the service and also since the clinic delivers the inmates of a home for unmarried white women.

Table IV indicates the proportion of patients in the series who had had previous abortions, and also the number of abortions which they had. It will be noted that almost two-fifths (39.08 per cent) of the total patients had miscarried one or more times previously, the incidence being highest in the missed abortion group (48.39 per cent) and lowest in the spontaneous type (32.92 per cent). Excluding primiparæ, we obtained the high figure of 46.62 per cent previous abortions. The majority of these patients have a history of only one previous abortion, but over one-fifth of them had had three or more. Furthermore, the incidence of this latter type of patient was much higher in the operative than in the spontaneous group, the percentages being 24.54 and 14.29, respectively. Four patients in the total series claimed to have had 10 or more abortions.

On investigating the complete obstetrical history of the patients in this series, excluding those

TABLE V.—INTERVAL

Time since last delivery	Spontaneous %	Operative %	Missed %	Therapeutic %	Total %
Less than 1 year	47.32	43.10	52.63	47.41	45.18
1 year	22.32	27.48	36.84	21.48	25.51
2 years	12.20	11.55	10.53	10.37	11.80
3 years	5.36	7.85	0.00	7.41	6.60
4 years and over	12.80	9.93	0.00	13.33	10.91

(Excluding primiparæ and unknown)

TABLE VI.—DURATION OF PREGNANCY

Duration	Spontaneous—%	Operative—%	Missed %	Therapeutic—%	Spontaneous and operative only Total—%
1– 4 weeks	0.49	2.40	0.00	0.00	1.58
5– 8 weeks	7.64	15.90	0.00	12.42	12.35
9–12 weeks	22.66	34.57	11.54	31.68	29.46
13–16 weeks	19.21	25.14	3.85	21.74	22.60
17–20 weeks	17.98	12.57	23.08	15.53	14.89
21–24 weeks	14.04	5.18	3.85	11.18	8.98
25 weeks and over	17.98	4.24	57.69	7.45	10.13
Mean duration	16 w. 5 d.	12 w. 4 d.	24 w. 0 d.	14 w. 1 d.	14 w. 3 d.

with therapeutic abortion, it was found that 39.51 per cent of the total pregnancies had terminated prior to a period of viability of the fetus. It is not our contention that this rate of 2 out of 5 pregnancies terminating as abortions holds for the general childbearing population. It is, however, our impression that it may be characteristic for a clinic population composed of women from the tenement districts of a large city, who begin bearing children early and repeat their pregnancies at close intervals.

Table V gives the interval between last pregnancy and one ending in abortion.

It has been suggested that the abortion rate increases in women repeating the childbearing process at frequent intervals. In the series under analysis, containing 83 per cent multiparæ, the large majority of patients had undergone a previous pregnancy recently. Thus 45 per cent had been delivered less than 1 year and 70 per cent less than 2 years prior to the gestation terminating in abortion. This not only indicates the fertility and close spacing of pregnancies in women of this type, but is, in our opinion, suggestive evidence of an increased abortion rate among them. In a similar series in which the pregnancy went to term, we found the conception occurring within a year of the previous delivery in only 30 per cent.

TABLE VII.—DURATION OF SYMPTOMS BEFORE COMPLETION OF ABORTION

Duration	Spontaneous—%	Operative—%	Missed %	Spontaneous and operative only Total—%
1– 4 weeks	50.94	59.42	20.00	55.22
5– 8 weeks	32.08	26.81	70.00	30.35
9–12 weeks	13.21	7.25	0.00	8.46
13 weeks and over	3.78	6.52	10.00	5.97
Mean duration	4 w. 4 d.	4 w. 3 d.	6 w. 3 d.	4 w. 4 d

Table VI indicates the time interval in weeks between the onset of the last regular menstrual period and the completion of abortion. It will be noted that the incidence of cases occurring in the first 8 weeks was more than twice as high in the operative (18.30 per cent) as in the spontaneous (8.13 per cent) group. Conversely 50.00 per cent of the spontaneous abortions occurred after the fourth lunar month, as contrasted with 21.99 per cent for the operative type. The mean interval was 16 weeks 5 days for the spontaneous group, as contrasted with 12 weeks 4 days for the operative, while for missed abortions 24 weeks elapsed. It is interesting to note that for the three groups —spontaneous, operative, and missed—the total duration was closely in terms of lunar months, which might be interpreted in terms of the "menstrual wave" as an associated factor.

Table VII indicates the interval between the onset of symptoms, lower abdominal cramps and bleeding, and the time of completion of the abortion. Little difference was noted between the spontaneous and operative types, but for missed abortion 6 weeks elapsed between onset of premonitory signs and the expulsion of the ovum. In one-seventh of the total cases, excluding missed abortion, more than 8 weeks elapsed, in many instances probably indicating a prolonged period of retention of the product of conception subsequent to death of the fetus.

Number of days of hospitalization. Nine days was the average term of hospitalization required for the spontaneous, operative, and missed abortion groups. In the therapeutic type the period was necessarily longer (21 days), because of the medical complications which had been the indication for the premature termination of the pregnancy. Ten per cent of the patients with spontaneous or operative completion had to be kept in bed for over 2 weeks, and 5 per cent for 3 weeks or more. In several instances prolonged hospitalization of 50 days or more was necessary because of infec-

TABLE VIII.—INTRAPARTUM INFECTION

	Per cent of total cases
Spontaneous	16.64
Operative	24.08
Missed	17.07
Therapeutic	2.44
Total	21.10

TABLE IX.—PUERPERAL MORBIDITY

Puerperium	Spontaneous, %	Operative %	Missed %	Therapeutic, %	Total %
Afebrile	81.78	78.68	73.17	60.98	79.75
Febrile, puerperal infection	15.60	20.65	24.39	19.16	18.80
Febrile, other causes	2.23	0.59	2.44	19.51	1.25
Died, no puerperium	0.39	0.08	0.00	0.35	0.20

tion, and 3 patients were observed for more than 3 months. These figures are included to emphasize the importance of the abortion problem economically to both the patient and the hospital.

The definition of intrapartum infection employed at the clinic is a temperature of 100.4 degrees F. or above, occurring prior to the completion of abortion and not due to extragenital causes. The clinic policy has been one of noninterference in cases of incomplete infected abortion, unless necessitated by hemorrhage, until clinical signs of the infection have subsided. It will be seen from Table VIII that one-sixth of the spontaneous and one-fourth of the operative cases manifested a febrile reaction prior to completion. Excluding therapeutic abortion, the mean incidence of intrapartum infection was 21.10 per cent, which may be contrasted with the figure of 2.55 per cent occurring in patients delivered at or near term.

It is the custom of the clinic to diagnose puerperal infection clinically in the presence of fever (100.4 degrees F., or above) on 2 days of the puerperium, not necessarily successive, excluding the first 24 hours after delivery and after having ruled out other causes, such as pyelitis or respiratory infection. It will be seen from Table IX that following abortion the puerperium was febrile due to puerperal infection in 18.80 per cent of the cases, the incidence being higher in the operative group than when completion was spontaneous. This figure would seem to compare favorably with an incidence of 17.50 per cent infection following delivery at or near term. However, the general clinic population is made up almost equally of white and black patients with puerperal infection occurring much more frequently among the latter, whereas in the abortion series the whites outnumber the blacks two to one. Therefore, in our experience, the chances of infection seem to be greater following abortion than delivery at term.

TABLE X.—INDICATIONS FOR OPERATION

Indication	Operative %	Missed %	Therapeutic—%
Inevitable abortion	3.66	5.00	0.00
Incomplete abortion	43.40	10.00	.....
Missed abortion	.....	30.00	.....
Hemorrhage	51.03	55.00	.....
Prolapsed cord or fetal part	0.48	.....	.....
Infection	0.80	.....	.....
Toxemia	.....	.....	40.56
Cardiac disease	.....	.....	13.33
Tuberculosis	.....	.....	10.00
Psychiatric disease	.....	.....	17.22
Pyelitis	.....	.....	4.44
Other conditions	.....	.....	14.44
Information incomplete	0.63	.....	.....

Incidence of admitted criminal procedures. Excluding cases of therapeutic abortion, the incidence of admitted criminal procedures among the patients of the series was 8.97 per cent, and was slightly lower in the single than in the married group. To what extent this figure represents the true picture is impossible to state, but in view of the generally known difficulty in procuring such an admission from the patient, it is probably far too low. In our experience it is extremely rare for a colored woman to induce an abortion upon herself, or to have such a procedure done by midwife or doctor. The great majority of admitted criminal attempts were in the white portion of the series, and for them the incidence was 14 per cent.

In well over half of the total admitted criminal abortions the method employed was the introduction of a bougie or rubber catheter, while a slippery elm stick was used in about a quarter of the cases. Two other methods admitted by a number of the patients were the introduction of a sound, or other metal instrument, and the insertion of a "sea tangle tent." A pencil, hatpin, nut-pick or glass rod was used by the occasional patient and one woman induced abortion by the intra-uterine injection of turpentine.

The indications for surgical interference in the operative and missed abortion groups, together with the disease conditions forming the basis for induction of the therapeutic abortions, are shown in Table X. It will be noted that hemorrhage of sufficient degree to necessitate emptying the uterus occurred in over half the cases of operative and missed abortion. Infection was the indication for operation in only 0.80 per cent, which illustrates the conservative policy employed by the clinic in this type of case. The four main indications for the induction of therapeutic abortion were toxemia, including nephritis and toxemic

TABLE XI.—CONDITION AT TIME OF OPERATION (FEBRILE OR AFEBRILE)

Condition at time of operation	Operative %	Missed %	Therapeutic—%
Febrile	13.04	15.00	5.00
Afebrile	86.80	85.00	95.00
Information lacking	0.16	0.00	0.00

TABLE XII.—INTRA-UTERINE CULTURES

Organisms found	Per cent	
Hemolytic streptococcus	7.83	
Aerobic non-hemolytic streptococcus	26.96	
Anaerobic streptococcus	35.65	
Streptococcus viridans	2.61	
Undifferentiated streptococcus	1.74	
Total streptococcus		74.78
Staphylococcus aureus	3.48	
Staphylococcus albus	22.61	
Undifferentiated staphylococcus	6.96	
Total staphylococcus		33.05
Bacillus coli	13.04	
Bacillus welchii	3.48	
Bacillus pseudonecrophorus	1.74	
Gonococcus	0.87	
Diphtheroids alone	2.61	
Undifferentiated bacteria alone	4.35	

vomiting; cardiac disease; tuberculosis; and psychiatric conditions, such as epilepsy, psychoses, and mental deficiency. In the group listed "other conditions" are included such miscellaneous factors as primary anemia, hydatidiform mole, hyperthyroidism, the fear of a third microcephalic child, etc.

Table XI is included to indicate that, despite the clinic policy of the avoidance of operative procedures in the presence of intra-uterine infection, bleeding was sufficient to necessitate completion of the process in 13 per cent of the operative and 15 per cent of the missed abortions which were infected. Pyelitis was the cause of fever in most of the 5 per cent similarly shown for the therapeutic cases. It is our opinion that intra-uterine manipulation in the presence of frank infection materially increases the hazards to the patient in terms of spread of the process.

An intra-uterine culture was taken in most instances prior to operation, when such procedures were necessary in the presence of fever. Cultures were also done whenever infection developed after abortion. Table XII indicates the bacteriological findings from cultures taken on the four types of cases in the series. Comment on this table seems unnecessary except to state that the percentage incidence of organisms found agrees rather closely with findings similarly obtained from a series of cultures on patients with clinical puerperal infection following delivery at or near term. Only two differences manifested themselves; the incidence of anaerobic streptococcus was lower and that of the colon bacillus higher in the abortion than in the term delivery group.

TABLE XIII.—DEATHS

Total deaths	Spontaneous —%	Operative %	Missed %	Therapeutic %	Total %
Afebrile on admission	0.524	0.669	0.000	4.878	0.600
Febrile on admission	0.917	1.171	2.439	0.348	1.100
Total	1.441	1.840	2.439	5.226	1.700
Deaths infection Afebrile on admission	0.000	0.418	0.000	1.046	0.250
Febrile on admission	0.917	1.171	2.439	0.000	1.100
Total	0.917	1.589	2.439	1.046	1.350

Of the total 2,287 cases of abortion in the series, there were 49 maternal deaths; of these 23 patients were febrile and 26 afebrile on admission to the hospital. The gross death rate, excluding therapeutic abortions, was 1.700 per cent and was highest in the missed and lowest in the spontaneous abortion group. However, the high rate in the missed abortion series may be discarded, since it represents one death from infection in a total of 41 cases. The mortality rate of 5.226 per cent in the therapeutic abortion group was to be expected and in most cases was due to the condition necessitating the interruption of pregnancy. Thus 19 of the deaths were due to unrelated causes, such as nephritis, toxemia, vomiting, cardiac disease, lobar pneumonia, carcinoma, and typhoid fever, leaving a mortality due to infection of 1.350 per cent, excluding therapeutic abortion. The patients constituting the series have been divided according to whether or not they showed signs of clinical infection in terms of fever at the time of admission to the hospital. This division is not an accurate one, since undoubtedly some of the women were infected prior to admission, although the condition had not yet progressed sufficiently to produce fever. Again excluding therapeutic abortions, the mortality rate due to infection, in patients afebrile on admission, was 0.250 per cent, or 1 in 400, with all the deaths occurring in the operative group. The higher rate of 1.100 per cent was obtained for the group "febrile on admission." It is interesting to note that in no instance was hemorrhage the immediate cause of death, although it undoubtedly contributed materially through a lowering of resistance to infection in a number of them.

DEDUCTIONS

The experience of this clinic has, in our opinion, substantiated the wisdom of the "hands off" policy in cases of infected abortion. Only when hemorrhage is sufficient to necessitate immediate emptying of the uterus should operative procedures be undertaken in such patients. During the waiting period supportive therapy and Fowler's position, supplemented by the use of frequent small blood transfusions (250 c.cm.) seems to offer the best results. Even in those patients who are admitted fever free, but in whom there is any question of previous intra-uterine manipulation, it is better to wait 24 to 48 hours in order that a latent infection, if present, may manifest itself. It is our conviction that any manipulation, and particularly instrumental curettage, materially increases the hazards to the patient, through removing the leucocytic defense wall within the uterus. During the early days of the clinic 2 deaths from septicemia occurred 48 hours after curettage in patients of this type. Moreover, for the protection of the physician, it is recommended that an intra-uterine culture be taken prior to any operative procedure in any suspicious or frankly infected case. The safety of digital as contrasted with instrumental curettage cannot be too highly emphasized.

In the missed abortion group, it is believed that waiting is again the most satisfactory policy. In a number of cases several weeks have elapsed between diagnosis and the actual passage of the product of conception, with operative procedures being employed only when necessitated by the physical or mental condition of the patient. Finally, when therapeutic abortion is necessary, it is important to defer operation if possible until the patient's general condition has reached its maximum improvement, and to perform the manipulation necessary under the most rigid surgical technique.

SUMMARY

An analysis has been made of the records of 2,287 cases of abortion treated by the Obstetrical Service of the Johns Hopkins Hospital over a period of 38 years. These cases have been divided according to type, as spontaneous, operative, missed, and therapeutic. The following is a summary of the points resulting from this analysis.

Abortions of all types comprised 7.60 per cent of the total clinic admissions in a series of over 30,000 patients observed by the service. Omitting pregnancies terminated for therapeutic reasons, 38.15 per cent of the abortions were completed spontaneously and 59.80 per cent by operative means, while 2.05 per cent were cases of "missed" abortion. The general clinic population is composed about equally of white and black patients, while for the abortion series 63.45 per cent were white and 36.55 per cent black. A definite racial difference was noted according to the type of abortion, and the percentages of white patients were 52.69, 65.85, and 70.23 for the spontaneous, missed, and operative groups, respectively. The mean age of patients in this abortion series was 3 years 7 months greater than that of the general clinic population. The average patient with spontaneous abortion was 25 years 5 months old, and 28 years 9 months in the operative group. Only 17.20 per cent of the patients with abortion were pregnant for the first time, although primigravidæ comprise 54.69 per cent of the general clinic population. The incidence of primiparæ in the operative group was only 12 per cent, as contrasted with the figures of 22 and 25 per cent for the missed and spontaneous types, respectively. Conversely, 38 per cent of the operative abortion patients had had 5 or more previous pregnancies, while this was true in only 24 per cent of the spontaneous cases. Thirty-nine and eight-hundredths per cent of the patients had had one or more previous abortions, and excluding primiparæ, 46.62 per cent. The lowest incidence was in the spontaneous, and the highest in the missed abortion group. Approximately one-fourth of the patients with previous abortion in the operative group had had three or more, whereas this was true of only one-seventh of the spontaneous cases. The complete obstetrical history of the patients in the series was analyzed, and it was found that 39.51 per cent of the total pregnancies had terminated prior to the period of viability for the child. Excluding primiparæ, 45.18 per cent of the patients had had a pregnancy less than a year prior to the one ending in abortion, and 70.69 per cent of them less than 2 years. Only 11 per cent of the women had not been pregnant within the previous 4 years. The mean duration of pregnancy at the time of completion of the abortion was 14 weeks 3 days, and was 4 weeks longer in the spontaneous than in the operative group. The average duration of symptoms (abdominal cramps or bleeding) before completion of the abortion was 4 weeks 4 days. Intrapartum infection, in terms of temperature elevation to 100.4 degrees F. or above prior to the completion of abortion was noted in 21.10 per cent of the total series, and was much more common in the operative than in the spontaneous group. Only 2.44 per cent of the abortions induced for therapeutic reasons evidenced intrapartum infection, and this incidence is almost identical with that occurring in patients delivered at or near

term. Allowing for the increased rate of puerperal infection found in black as contrasted with white women, the incidence of this complication was somewhat higher in this series than in the clinic's experience with patients delivered at term. Puerperal infection occurred most commonly in the missed abortion group and least so in the spontaneous group. Nineteen per cent of the patients with therapeutic abortion had febrile puerperia, due to intra-uterine infection. Only 9 per cent of the patients in the series admitted criminal attempts at induction of abortion. It is our experience that the negress makes such attempts very rarely and omitting them, the incidence becomes 14 per cent. The indication for operative completion of abortion was hemorrhage in over half of the cases in the operative and missed groups. Toxemia, psychiatric disease, cardiac disease, and tuberculosis, in the order given, were the major indications for the induction of therapeutic abortions.

Although it is a matter of clinic policy not to interfere in cases of infected abortion, yet in approximately one-seventh of the operative and missed groups, hemorrhage was sufficient to necessitate emptying the uterus in the presence of fever. Some variety of streptococcus was obtained from 75 per cent of the intra-uterine cultures taken on infected cases. The bacteria found, as well as the incidence of each type, were approximately the same as in a series of patients with puerperal infection following delivery at or near term, except that the anaerobic streptococcus occurred less frequently and the colon bacillus more often in the abortion series. The gross mortality rate for the series, excluding therapeutic abortion, was 1.700 per cent, and was higher in the operative than in the spontaneous group. The death rate due to infection was 1.350 per cent and among patients afebrile at the time of admission to the hospital was 0.250 per cent. It is the opinion of this clinic that a conservative policy of non-interference in the presence of obvious infection offers the best results in cases of abortion. Repeated small transfusions of blood seem to have a beneficial therapeutic effect.

EDITORIALS

SURGERY, GYNECOLOGY AND OBSTETRICS

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JULY, 1936

THE BRAIN TUMOR REGISTRY

IN an article recently published[1], Mr. Hugh Cairns of London has made a careful study of the intracranial tumor cases which came under his supervision while acting as Dr. Harvey Cushing's resident assistant at the Peter Bent Brigham Hospital in 1926–1927.

This study calls attention to the unique collection of over 2,000 brain tumors with the microscopical preparations and records pertaining thereto which, under the custodianship of Dr. Louise Eisenhardt, has been set up in the Pathological Department of the Yale School of Medicine as the basis of an enlarging source of information concerning lesions of this special type. It also gives an indication of the purposes to which the collection may be put and emphasizes the manner in which it is certain to become increasingly valuable for future studies of a similar kind in years to come.

[1]Cairns, H. The ultimate results of operations for intracranial tumours. A study of a series of cases after a nine-year interval. Yale J. Biol. & Med., 1936, 8: 421.

There is much still to be learned about brain tumors, many of which have not as yet even been satisfactorily classified. It is only by continued study that the life history of one after another of the many varieties can be fully worked out so that the expectation of life, and the relative freedom from incapacitation after operation of a given type of tumor found in a particular situation can be known at the time it is first brought to view. Not until the behavior of every kind of tumor is thoroughly understood by the person who attempts surgically to deal with them can it be decided which particular form of intervention, whether by extirpation or irradiation, will give the lowest operative mortality and at the same time the longest survival period with the least impairment of the afflicted individual's intellectual and physical capacity to earn his livelihood.

Mr. Cairns' paper represents a new type of report of surgical end-results and it is particularly important in the case of pathological lesions of the sort with which he has dealt. Surgeons heretofore have been satisfied to work out the operative mortality percentages and the survival periods for tumors of special kinds, but to try to determine after a given period what the survivors have been good for and to what degree the spared life has been worth living is something altogether new. Such a study is only possible when records are of the best and when the relation of patients and surgeon has been on an unusually intimate basis.

In his prefatory note, Dr. Cushing refers to certain matters which might be regarded as controversial, one of them being the question

of to what extent outside discrimination and selection of cases might affect a surgeon's mortality percentages and survival periods. He would probably be the first to acknowledge that his known interest in pituitary disorders led patients with adenomas to frequent his clinic, doubtless on the family doctor's advice; but beyond this it is difficult to believe that there was any discrimination made in the type of cases recommended to the Brigham clinic for diagnosis and treatment. Certainly those who worked there know that no discrimination was made between favorable and unfavorable cases once the patients arrived. It was most unusual for the neurologists, ophthalmologists, or physicians who referred patients to do more than make a tentative localizing diagnosis except, naturally enough, in the case of acoustic tumors, in which the localizing diagnosis usually indicated the nature of the tumor as well.

It should be remembered, also, that until a pathological classification was worked out upon the tumors encountered in Cushing's clinic, no attempt had been made to distinguish between different types of gliomas, either before or after operation. Until tumors were classified and the life history of some of them worked out, there was no possibility of discriminating before operation between favorable and unfavorable cases. It was felt that every case of intracranial tumor called for an operation; and some still believe in following this rule today even in the case of the highly malignant cerebral glioblastoma multiforme and the cerebellar medulloblastoma.

Cairns' study of 157 patients with verified intracranial tumors operated upon in 1926–1927 by Dr. Cushing covers the pathological type of the tumor, its situation, and the condition of each patient seven to nine years after operation. Sixty-three patients were still alive and 37 of those were living useful lives. The best late results were obtained in cerebellar astrocytomas, cholesteatomas, meningiomas, pituitary adenomas, and in a small proportion of acoustic neurinomas.

The illuminating "longest known survival" figures which Dr. Eisenhardt has added to Mr. Cairns' tables showing a four year survival for a glioblastoma and a seven year plus survival for a medulloblastoma makes one feel that in view of his inability to make an absolutely correct pre-operative pathological diagnosis, a surgeon is scarcely justified in refusing operation because a tumor is presumably malignant and the surgical exposure is known to have a high percentage of postoperative fatalities.

RÔLE OF PRELIMINARY MEDICATION IN ANESTHESIA

PRELIMINARY medication has so developed that now it is a benefit to surgeons, obstetricians, patients, and especially to anesthetists. The patient is benefited by obtaining a good rest the night before the operation, his energy is conserved, and he is brought to the operating room far less fearful and apprehensive than formerly was possible without depressing his vitality. The wide clinical application of the barbiturates has resulted in the development of special preparations of them so that now specific results can be obtained. It is recognized that when these drugs are themselves not used to produce the anesthesia, fortunately the dose of the drug, rather than the method of administration is important. It has been found that the use of small doses of barbiturates, together with morphine and atropine, in preliminary medication, permit wider choice of anesthetic agents than was possible before the barbiturates came into use. If preliminary medication is given, patients do not complain much about the administration of local anesthetic

agents, whether they are given for local, spinal, or regional anesthesia. In the field of local anesthesia, the barbiturates are certainly the agents of choice for preliminary medication, because they tend to neutralize one of the toxic effects of local anesthetic agents; namely, their tendency to cause convulsions. A further benefit in the use of the barbiturates is that they increase the tolerance of the patient for the epinephrine which is usually combined with the local anesthetic agent. Patients who are fearful and those whose fear continues for many hours preoperatively do not tolerate epinephrine well.

Since preliminary medication has been employed, it has been possible to give gaseous anesthetic agents combined with amounts of ether smaller than were necessary before, and ether, when administered by the drop method, can be used in smaller quantities. The anesthetist is able to produce anesthesia, with quiet breathing and relaxation, more quickly and more easily and without producing as profound a degree of narcosis. Other factors that help to accomplish these same results, but which cannot be stressed here, are the use of Magill's intratracheal tube, the use of balanced anesthesia, which is the combination of small amounts of several anesthetic agents each given by an appropriate method, and the use of tribromethyl alcohol in amylene hydrate (avertin) for basal anesthesia. Although this use of avertin might be considered under preliminary medication, and its benefits are recognized, it is not included in this discussion.

The barbiturates, when administered at the proper time in labor, have been of such benefit that they are very widely used. The obstetrician has found that small doses, followed by administration of anesthetic agents, have been beneficial in most cases. The greatest good for the greatest number has been brought about by the judicious use of drugs that have borne part of the burden of placing the patient in a condition in which anesthesia or analgesia could be produced with a minimum of disturbance on the part of the patient, and with a minimum of effort on the part of the anesthetist, the surgeon, and the obstetrician.

Many drugs have been used for sedation and for the average person relatively inexpensive drugs are adequate. The fact that some of the more modern drugs are expensive is usually the argument given against prescribing them. Experience leads to the belief, however, that modern pharmaceutical chemists have kept pace with modern needs and that some recently developed drugs are definitely superior to older ones. There is a difference, clinically, in the effect of two barbiturates, such as barbital and pentobarbital sodium, and these differences must be kept in mind, especially in the management of surgical patients. Relatively short periods of rest separated by periods of relative freedom from the effects of medication are invaluable to those in charge of the postoperative care of patients. Prolonged periods of sleep or unconsciousness might lead to confusion as to whether the sleep or unconsciousness was attributable to the prolonged action of a drug or to some new pathological condition.

The combined effect of a barbiturate and morphine is to reduce the minute volume of respiration, and for that and other reasons, such as the idiosyncrasy of certain individuals to certain drugs, a routine dose should not be employed. The effect desired is quiet and freedom from fear, but not inability of the patient to walk alone or to answer questions. If a general anesthetic agent is administered following heavy preliminary medication, it is not uncommon for respiration to be greatly depressed before relaxation can be produced. Under such circumstances the surgical pro-

cedures may be interfered with. This is especially true when anesthesia is produced by administration of ether by the open drop method but depression of respiration is of much less importance when block anesthesia or local infiltration is combined with gas anesthesia. The use of atropine is of value when anesthesia is produced by inhalation. The dose, however, need not be large; for the average adult it is about 1/150 grain (0.0004 gram). It is especially useful when children are anesthetized; depending on their weight, they may tolerate a dose of 1/300 grain (0.0002 gram), which is a relatively greater dose for their size than that given to adults.

Aside from the hypnotic effect of barbiturates, there is recent experimental evidence which seems to corroborate clinical impressions that the onset of shock is usually delayed if barbiturates have been used. However, barbiturates given preliminary to blood transfusion and to intravenous administration of solutions make the procedures easier for the recipients to tolerate and may minimize the untoward reactions. Recent work, also, has tended to show that the effects of particular anesthetic agents are especially influenced by particular kinds of preliminary medication and that, accordingly, the anesthetic agent and the method of its administration should be chosen with knowledge of what preliminary medication has been used. JOHN S. LUNDY.

MEMOIRS

JOHN RIDLON

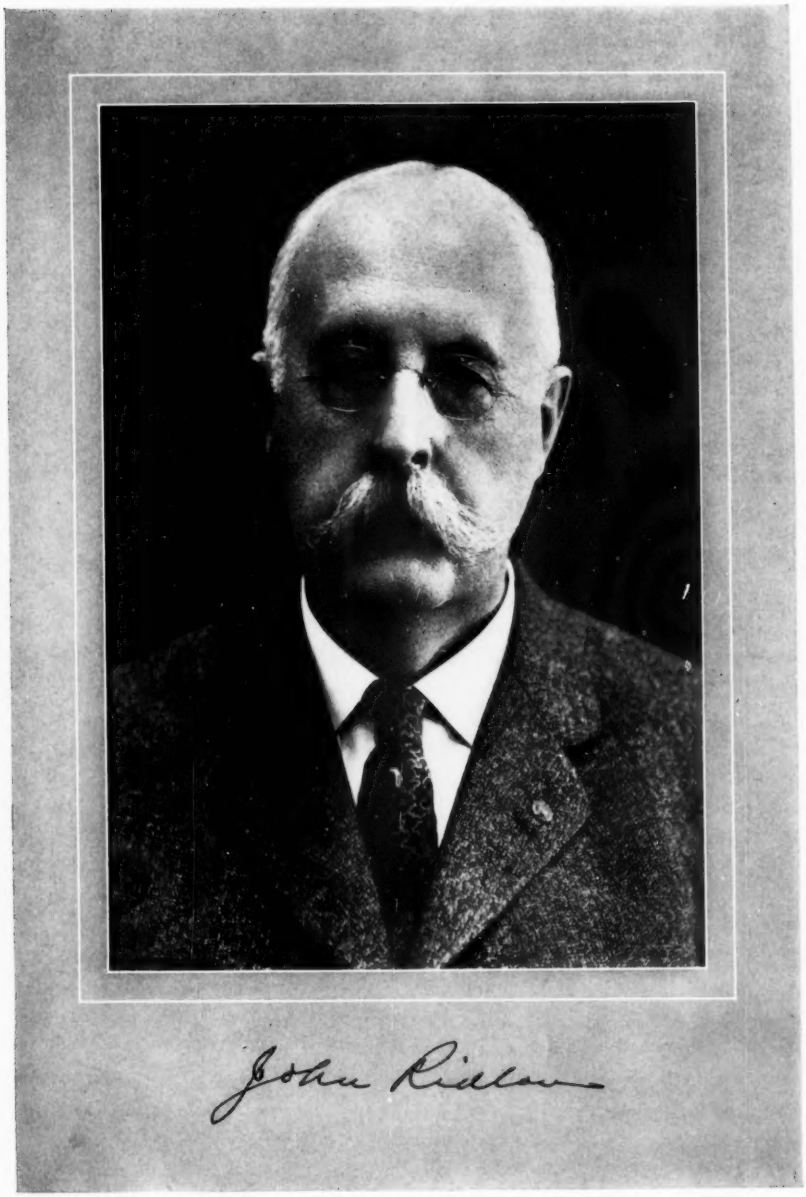
JOHN RIDLON was born in the township of Clarendon, Rutland County, Vermont, on November 24, 1852. He was one of three boys, but the two others died in infancy. His father, Noel Potter Ridlon, was a farmer who became a dairyman just before the Civil War. His mother was Nancy Bromley Hulett Ridlon, of Pawlet, one of thirteen children. Dr. Ridlon always spoke highly of his Grandmother Ridlon whose husband died at the early age of fifty-five, and who with forty acres of land and about eight hundred dollars in money at interest, raised eight children and five grandchildren.

When John was fourteen his father was killed in a railway accident while driving home from Rutland. The next year he and his mother left the farm for Poultney, Vermont, where he attended a commercial college. Not long afterward they went to Marengo, Illinois, making the trip over the New York Central and Michigan Central railroads before the days of sleepers, diners, or even wash basins on the train. At this time there came an opportunity to sell the Vermont farm which was supposed to contain marble, and John and his mother were left in comfortable possession of about fifteen thousand dollars.

During the next few years Ridlon worked at various times as book salesman, grocery clerk, and helper to a civil engineering corps. His mother remarried. After contracting malaria and losing eighteen pounds in weight, John returned to Vermont to attend the Vermont Central Institute and later Tufts College. Through a miscarriage of college justice, he was expelled from Tufts at the end of his sophomore year and so went to the University of Chicago, graduating in 1875. An early indication of intellectual independence was his class oration on "The Infallibility of the Pope"; its departure from orthodoxy creating a stir in that Baptist institution.

At his various colleges, Ridlon played baseball, taught boxing and fencing, organized a debating club, started a library, and pulled No. 5 on the crew. He also played bass viol in the orchestra and became a member of Theta Delta Chi, Delta Kappa Epsilon, and other college societies. In 1899 he was recalled to Tufts to receive an Honorary M.A. degree, and again in 1926 to be awarded the degree of Sc.B.

In 1875 Ridlon entered the College of Physicians and Surgeons in New York with Prof. E. G. Seguin as his preceptor. When he graduated, March 1, 1878, he



John Ridlon

UNIV. OF MICH.

was Class Marshal. He obtained a staff position at St. Luke's Hospital in New York, serving as house officer for two years. On June 4, 1879, he married Emily Caroline Robinson of Newport, Rhode Island. Mrs. Ridlon's father was a sea captain of many years' service. From him they inherited the home at No. 1 Sea View Avenue in Newport where were spent the last years of Dr. Ridlon's life.

Dr. Ridlon left St. Luke's Hospital in 1880 at the time their first child was born. For the next two years he was in general practice at 152nd Street and St. Nicholas Avenue. In 1880 also he received his first orthopedic appointment as assistant to Dr. Newton M. Shaffer at St. Luke's Hospital, going later to the New York Orthopedic Hospital and Dispensary.

Dr. Ridlon was one of the first in America to be attracted to the work of Hugh Owen Thomas in Liverpool. He went to see Thomas' work first hand, and became one of his very few close friends and a lifelong friend and associate of Thomas' nephew and successor, Sir Robert Jones. When Dr. Ridlon visited Mr. Thomas first he expressed skepticism as to the results claimed for the Thomas traction splints in hip, knee, and ankle disease. Mr. Thomas was able to convince him of their utility and efficiency, however, and Dr. Ridlon became and remained the leading American exponent of Thomas' principles of treatment for diseases and injuries of the extremities. Thomas' splints and the principles he taught received world wide recognition during the World War and led to the saving of thousands of lives and limbs.

When Dr. Ridlon returned from Liverpool in 1887 he made and applied at St. Luke's Hospital the first Thomas hip splint ever to be used in this country for tuberculous hip disease. Dr. Shaffer ordered the splint removed but Dr. Ridlon refused to remove it on the ground that he was responsible for the welfare of the patient. At the end of his year's service Dr. Shaffer prevented his reappointment and Dr. Ridlon went with Dr. McBurney to the Vanderbilt Clinic. A little later, when Dr. Gibney was elected to a professorship which Dr. Ridlon had expected, he moved, in 1889, to Chicago. Concerning the New York controversy over the use of the Thomas splint, it is interesting to read in Dr. Judson's book (1905): "Flexion and abduction [in hip disease] are rapidly reduced . . . by the use of Mr. Thomas' hip splint in the skillful hands of Dr. Ridlon."

In June, 1890, Dr. Ridlon returned to Europe to assist in the organization of an orthopedic section of the International Medical Congress. He called upon Grattan (of the osteoclast) at Cork, Thomas and Jones at Liverpool, George Arthur Wright at Manchester, Florian Beely of Berlin, and many others. Dr. Ridlon and T. L. Stedman of New York had been commissioned by the *New York Medical Record* to report the Congress. Dr. Ridlon gathered the news while Dr. Stedman, from his room at the Kaiserhof Hotel, cabled fifteen thousand words to New York, thus "scooping" all other American medical journals by two weeks!

When Dr. Ridlon came to Chicago in 1889 he was made instructor in orthopedic surgery at Northwestern University by Dr. N. S. Davis I. A year later he was made professor and served for sixteen years. Subsequently, he was professor at Rush for three years, professor and secretary of the faculty at the Woman's Medical College for three years, orthopedic surgeon at St. Luke's Hospital for ten years, and attending orthopedic surgeon for a time at Michael Reese Hospital. He organized the orthopedic services of the Evanston Hospital and the Home for Destitute Crippled Children. He was chief surgeon at the latter institution for twenty years, leaving there with regret and a tinge of bitterness at being displaced by younger men. At the time of his retirement, however, he was made consultant and life member of the corporation.

Dr. Ridlon was a charter member of the American Orthopedic Association (1887). At its tenth meeting, he was president. In his presidential address, he called attention to the presence of fifty-two members from sixteen cities and spoke of the value to the association of having not only those from the larger centers with abundant opportunities "to see" but of having also those from the smaller towns who had time "to think." It is significant that among those from the "smaller towns" at that meeting were Gillette of St. Paul, Griffith of Kansas City, Moore of Minneapolis, Packard from Denver, Sherman from San Francisco, Steele from St. Louis, and Weigel from Rochester, all of whom have placed their names permanently upon the roll of honor in orthopedic surgery.

That Dr. Ridlon dominated the affairs of the American Orthopedic Association for many years was not only charged by others but admitted by himself. Indeed he said: "When I returned from the International Medical Congress (in 1890), I rushed back to New York to be in time for the meeting . . . in Philadelphia. DeForest Willard was president and George F. Ryan was secretary. I proceeded to elect A. B. Judson as president and myself as secretary. At that time the secretary was also treasurer and editor of the *Transactions*. I served as secretary for sixteen years and one year as president. I was counted as 'Boss' of the Association because I elected every officer except Weigel during that time." Dr. Ridlon later completed the unexpired "war terms" as secretary for Ralph Fitch of Buffalo in 1915 and for the writer in 1918.

For several years Dr. Ridlon served on the editorial staff of SURGERY, GYNECOLOGY AND OBSTETRICS and did much to assist the staff in building up the journal.

At sixty-five, Dr. Ridlon reported September 22, 1917 for active military duty at Fort Benjamin Harrison. He had already joined the Medical Reserve Corps in 1909 and had attended a Plattsburg Medical Training Camp in 1916. During his military service, Dr. Ridlon was instructor and inspector in orthopedic surgery at various forts and camps, finally becoming instructor in the Army Medical School from which he was honorably discharged February 8, 1919. Later he joined the Public Health Reserve, serving at the U. S. Marine Hospital and later

at the Veterans Hospital from which he was transferred to the Edward Hines Jr. Hospital in Chicago when that institution was established.

One of Dr. Ridlon's outstanding characteristics was his generosity both professionally and financially to younger men. There was never a time when he would not give his energy or his money to assist especially one who was disposed to devote himself to the study and practice of orthopedic surgery. Many of the men of rising prominence in the middle west and even the far west have been Dr. Ridlon's students in orthopedic surgery, a number having been undergraduates during his professorship at Northwestern University.

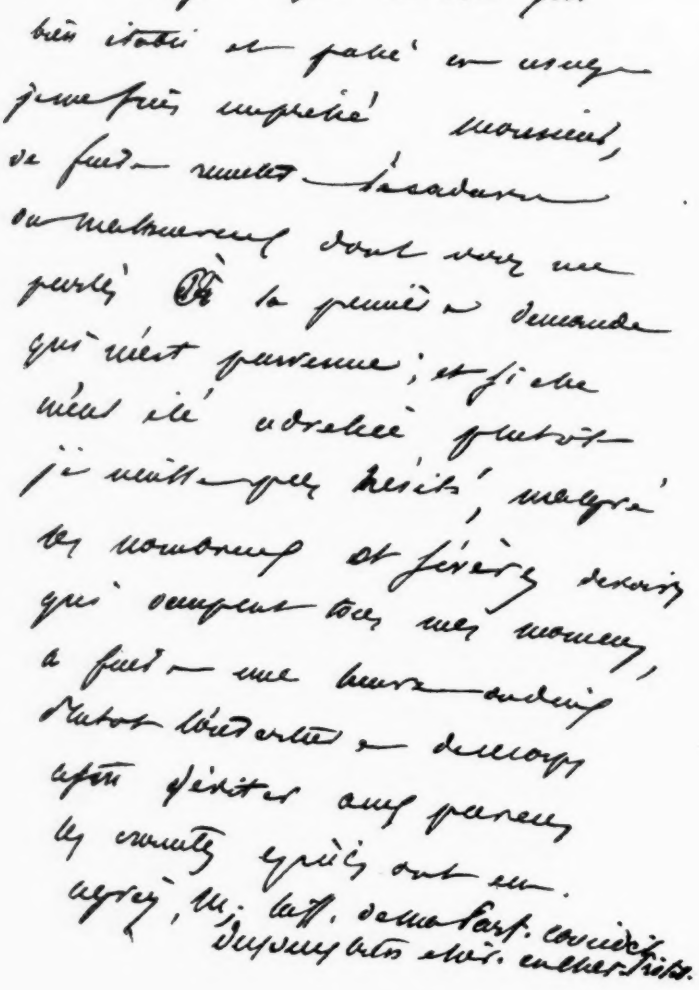
In 1923 it was the privilege and pleasure of this group of students and a few other friends of Dr. Ridlon to gather in Chicago and to present to him and Mrs. Ridlon the fine portrait painted by Mr. Carl Bohnen which hangs in the Archibald Church Library of Northwestern University Medical School. At the close of the presentation exercises, Dr. Ridlon remarked that he realized for the first time that he had always had what he knew he had always wanted, namely, the friendship and regard of the men whom he had looked upon somewhat too formally as students and professional colleagues.

After 1928 Dr. Ridlon retired from practice in Chicago to make his home at Newport, Rhode Island. Even as he approached eighty years of age, however, he remained active. During 1931 he conducted an inspection of the school children of Newport for physical defects. He traveled to meetings of his orthopedic associates in Boston, New York, and elsewhere, and in 1933 was guest of honor at the Washington, D.C. meeting of the American Orthopedic Association under the presidency of Dr. Arthur Steindler. For several years he applied himself almost daily to typewriting notes regarding the personalities and surgical experiences of his earlier days. He kept alive an extensive correspondence with many of the men in orthopedic practice in whom he always maintained a keen personal and professional interest.

When he left Chicago, Dr. Ridlon distributed a small but choice collection of books on the history and practice of orthopedic surgery. Many of these are to be found now in the special collection accumulating under the direction of the writer in the library of the American College of Surgeons in Chicago. The forthcoming catalogue of this collection will contain many references to Dr. Ridlon and many quotations from his letters and conversations.

Dr. Ridlon's patients, pupils, and professional contemporaries will always hold him in high esteem. His devotion to his specialty and his ideals for the care of his patients were often expressed in criticism of those who fell short of his standards. Those who profited by his teaching and by the example of his methods, however, cannot but feel that they are much the better for his guidance, for his industry, and for his constant inspiration.

H. WINNETT ORR.



A facsimile of a portion of a letter written on April 14, 1818, by Guillaume Baron Dupuytren concerning an ordinance which granted the hospital staff the right to perform an autopsy, without the consent of the family, if such a procedure was judged necessary.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE book by Taussig[1] is one of a series of monographs dealing with the medical aspects of human fertility. It is sponsored by the National Committee on Maternal Health and represents a comprehensive review of the entire subject; its expressed purpose is to afford physicians, sociologists, and students of public health the facts needed to understand the ill effects of abortion on the physical well-being and moral integrity of the community.

The author has divided the material under four general headings: (1) history and background; (2) spontaneous abortion; (3) induced abortion; (4) social aspects of abortion. Included in the first section is an interesting chapter on abortion in domestic animals, prepared by W. L. Williams, in which comparable conditions in etiology to those in the human are described.

In the United States, it is estimated that about 681,600 abortions occur annually, in proportions of 1 to 25 births in urban, and 1 to 5 births in rural districts. Taussig points out that as a result of abortions, about 8,000 to 10,000 women die each year and many more are disabled by septic sequelæ. This mortality and morbidity is due largely to the fact that so large a proportion of abortions are induced illegally under most unfavorable conditions. In contrast, he cites the results of legalized abortions as performed in the United States of Soviet Russia. A chapter is devoted to "Legalized Abortion in the Soviet Union" and the author states, "No book on abortion written today can be complete without special consideration of the movement in Soviet Russia to legalize abortion." Under this plan, there were about 91,000 abortions performed in Moscow alone during 1931 with a death rate of only 1 in 10,000. In the past 4 years, however, they have noted the frequent occurrence of serious sequelæ—pelvic infections, endocrine and menstrual disturbances, ectopic pregnancy, sterility, and functional neuroses. As a result of the realization of this undesirable aftermath, a determined effort is now being made by the Soviet physicians to decrease the incidence of abortions and to encourage birth control, facilities for contraceptive advice being offered in organized "Prophylactariums." The Russian experiment has indeed furnished much food for thought.

In the chapter on the treatment of abortion, a review of the literature and an evaluation of results obtained in various countries is clearly interpreted. The conservative versus the radical surgical treatment is fully and fairly discussed by the author.

The book is splendidly written, well illustrated, and is free from errors. It is, indeed, a most valuable monograph which will doubtlessly be widely read by physicians in all fields of medicine.

IRVING F. STEIN.

[1] ABORTION; SPONTANEOUS AND INDUCED; MEDICAL AND SOCIAL ASPECTS. By Frederick J. Taussig, M.D., F.A.C.S. St. Louis: The C. V. Mosby Co., 1936.

A SECOND edition in three years speaks for the excellence of *Electrotherapy and Light Therapy*[2] by Kovacs. The book has been thoroughly revised; most of the new material is from laboratory and experimental observations.

The first two parts of this book present the physics of the different electrical currents, consider the apparatus for their production, explain their action on the body, describe the technique of their application, the indications and contra-indications for their use, and the possible dangers involved. Kovacs points out that the regulation of dosage in short-wave diathermy is at present an even more empirical procedure than in ordinary diathermy. Although the author indicates in several places that the reports of Schliephake await corroboration by competent observers, the conditions in which Schliephake obtained favorable results are enumerated. These claims contain such statements as "In purulent processes in the chest, purulent pneumonias, pulmonary abscesses and gangrene, pleural empyemas, complete resorption of the pus was effected in three to four weeks without any surgery." As this book is for students and general practitioners it would seem that such optimistic claims could be omitted.

In part three the physics of radiant energy, the effects of infra-red, luminous, and ultraviolet radiation; the clinical application of heliotherapy and the artificial sources of radiation are carefully considered. There is a complete discussion of the sources of ultra-violet radiation. It considers the newer sources of artificial radiation, the cold quartz and electrodeless high-frequency induction lamps, and notes that so far no clinical reports of results with controls have been published.

Part four is devoted to applied electrotherapy and light therapy in internal medical conditions, chronic arthritis, fibrositis, affections of the nervous system, bones, joints, muscle and tendons, in gynecological, genito-urinary and proctological conditions. The chapter on dermatological conditions is by Dr.

[2] ELECTROTHERAPY AND LIGHT THERAPY. By Richard Kovacs, M.D. 2d ed. Philadelphia: Lea & Febiger, 1935.

Joseph J. Eller, diseases on ear, nose and throat by Dr. Wallace Morrison.

This book can be recommended as the best textbook on electrotherapy. J. S. COULTER.

THE second part of the second half of the fourth volume of Stoeckel's *Handbuch der Gynaekologie*[1] devotes eleven hundred pages to the roentgen treatment of malignant tumors. This volume, like the first half which dealt with non-malignant tumors, is encyclopedic in character. It contains over two hundred pages of finely printed references of the entire world literature.

This work is open to the same criticisms which were voiced in connection with the first half of the work, which was written by the same authors. Wintz and Wittenbeck have made the work most cumbersome by virtue of the fact that it is too all-inclusive. The section on the methods of technique include all of the methods used in the major clinics of the world. Thus valuable space has been devoted to a tiresome and endless repetition of methods, many of which are antiquated and have been discarded. This attempt to make each section historically and referentially complete, makes this volume too ponderous for practical use. It loses its value even as an encyclopedia and reference work.

RALPH A. REIS.

[1]VEIT'S HANDBUCH DER GYNAEKOLOGIE. 3d rev. enl. ed. Edited by W. Stoeckel. Vol. iv. 2d half—Klinik der gynaekologischen Roentgentherapie. 2d part—Die Behandlung der boesartigen Geschwuelste. By H. Wintz and F. Wittenbeck. Munich: J. F. Bergmann, 1935.

IN his volume, devoted to war injuries,[2] Carl Franz discusses the following subjects: shock and collapse, injuries of the soft parts, suppurative and putrefactive wound infection, injuries of arteries and sites for ligation, injuries of peripheral nerves and the central nervous system, injuries and infections of joints, the technique of joint resection and disarticulation, gunshot fractures, injuries of the scalp, skull, face, mouth and eyes, injuries of the thoracic cage and abdomen.

It is obvious, of course, that the author does not intend this book as an exhaustive treatise on traumatic surgery or as a source of detailed instruction in the care of compound injuries, of plastic or neurologic surgery, which of course it certainly is not. To the uninitiated it offers a rather panoramic view of war surgery—its nature, its difficulties and failures—and above all, the vast diversifications of surgical situations that result from the battlefield.

J. R. BUCHBINDER.

[2]LEHRBUCH DER KRIEGSCHIRURGIE. By Dr. Carl Franz. 2d ed. enl. Berlin: Julius Springer, 1936.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

COLLECTED PAPERS OF THE MAYO CLINIC AND THE MAYO FOUNDATION. Edited by Richard M. Hewitt, B.A., M.A., M.D., Lloyd G. Potter and A.B. Nevling, M.D. Vol. 27. Philadelphia, London: W. B. Saunders Co., 1936.

DIE NACHBEHANDLUNG NACH OPERATIONEN; EIN LEHRBUCH IN VORLESUNGEN. By Prof. Dr. Paul Reichel. 3d ed. Munich: J. F. Bergmann, 1936.

THE SURGICAL TECHNIC OF ABDOMINAL OPERATIONS. By Julius L. Spivack, M.D. Chicago: S. B. Debour, 1936.

DISEASES OF THE NOSE, THROAT AND EAR; FOR PRACTITIONERS AND STUDENTS. Edited by A. Logan Turner, M.D., LL.D., F.R.C.S.E. Baltimore: William Wood & Co., 1936.

THE EXTRA-OCULAR MUSCLES; A CLINICAL STUDY OF NORMAL AND ABNORMAL OCULAR MOTILITY. By Luther C. Peter, A.M., M.D., Sc.D. Philadelphia: Lea & Febiger, 1936.

UROLOGY IN WOMEN; A HANDBOOK OF URINARY DISEASES IN THE FEMALE SEX. By E. Catherine Lewis, M.S.(Lond.), F.R.C.S.(Eng.). 2d ed. Baltimore: William Wood & Co., 1936.

PASSIVE VASCULAR EXERCISES; AND THE CONSERVATIVE MANAGEMENT OF OBLITERATIVE ARTERIAL DISEASES OF THE EXTREMITIES. By Louis G. Hermann, A.B., M.D. With a Foreword by Mont R. Reid, M.D. Philadelphia and London: J. B. Lippincott Co., 1936.

THE BABY AND GROWING CHILD; FEEDING AND HEALTH CARE FOR PHYSICIANS, MOTHERS, AND NURSES. By Louis Fischer, M.D. New York and London: Funk & Wagnalls Co., 1936.

SYPHILIS AND ITS TREATMENT. By William A. Hinton, M.D. New York: The Macmillan Co., 1936.

POST-GRADUATE SURGERY. Edited by Rodney Maingot, F.R.C.S.(Eng.). Vol. 2. New York: D. Appleton-Century Co., 1936.

ETUDE DE L'INFLUENCE DES GLANDES ENDOCRINES SUR LE SQUELETTE. By Dr. G. Coryn. Archives Internationales de Médecine Expérimentale. Vol. 11. Fasc. 1–2. Paris: Masson et Cie, 1936.

THE PATIENT AND THE WEATHER. By William F. Petersen, M.D. With the assistance of Margaret E. Milliken S.M. Volume 1. Part 2—Autonomic Integration. Ann Arbor, Mich.: Edwards Brothers, Inc., 1936.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

DONALD C. BALFOUR, Rochester, *President* EUGENE H. POOL, New York, *President-Elect*

HENRY P. BROWN, JR., *Chairman;* GILSON C. ENGEL, *Secretary, Committee on Arrangements*

THE 1936 CLINICAL CONGRESS IN PHILADELPHIA

THE surgeons of Philadelphia are planning largely for the twenty-sixth annual Clinical Congress of the American College of Surgeons to be held in that great medical center October 19–23, 1936. They will present a program of surgical clinics and demonstrations that will provide a complete showing of their clinical activities in all departments of surgery. The Committee on Arrangements is assured of the hearty co-operation of the clinicians at the five medical schools and more than thirty hospitals participating in the clinical program.

A preliminary clinical program was published in the June issue of this journal and the Bulletin of the College and will be republished in the August issue. The clinical program is to be further revised and amplified during the coming months as the work of the program committee progresses. Operative clinics and demonstrations in the hospitals are scheduled for the afternoon of Monday, October 19, beginning at 2 o'clock, and for the mornings and afternoons of each of the four following days. All departments of surgery will be represented therein—general surgery, gynecology and obstetrics, genito-urinary surgery, neurosurgery, orthopedics and surgery of the eye, ear, nose and throat.

The Committee plans to develop many special features in the clinical program including: (1) Cancer clinics demonstrating the treatment of cancer by surgery, radium and x-ray; (2) fracture clinics demonstrating modern methods in the treatment of fractures; (3) clinics in traumatic surgery presenting the newer methods of rehabilitation of the injured by surgery and physical therapy.

An extensive schedule of operative clinics and demonstrations at the hospitals that will be of particular interest to those who specialize in surgery of the eye, ear, nose and throat is being prepared by the sub-committee on ophthalmology and otolaryngology.

EVENING MEETINGS

The Executive Committee of the Board of Regents is preparing programs for the five evening scientific sessions to be held in Irvine Hall. At the presidential meeting on Monday evening, the first formal session of the Congress, Dr. Donald C. Balfour, the retiring president, will deliver an address, and Sir James Walton, of London, England, will give the second annual oration on surgery. At this session the new officers will be inaugurated: Dr. Eugene H. Pool, New York, president; Dr. Emile Holman, San Francisco, and Dr. George E. Wilson, Toronto, vice-presidents.

Dr. Eugene H. Pool will deliver the presidential address at the convocation of the College on Friday evening on which occasion the 1936 class of initiates will be received into Fellowship.

At sessions on Tuesday, Wednesday and Thursday evenings eminent surgeons of the United States and Canada with visiting surgeons from foreign countries will present papers on surgical subjects of present day importance. Among papers to be presented are the following:

The Treatment of Coronary Sclerosis and Angina Pectoris by Grafting a New Blood Supply to the Myocardium. CLAUDE S. BECK, Cleveland.

Treatment of Fracture of the Neck of the Femur by Internal Fixation. M. N. SMITH-PETERSEN, Boston.

Injuries of the Bones and Soft Tissues of the Face. VILRAY P. BLAIR, St. Louis.

Rationalizing Treatment in Acute Intestinal Obstruction. OWEN H. WANGENSTEEN, Minneapolis.

Chronic Intestinal Obstruction Due to Lesions of the Large Bowel. VERNON C. DAVID, Chicago.

The Combined Spleen Clinic: Results with Medical and Surgical Therapy in Splenopathies. ALLEN O. WHIPPLE, New York.

Fracture Oration: The Essential Features of Fractures of the Shoulder. GEORGE E. WILSON, Toronto.

The Management of Severe Hyperthyroidism. FRANK H. LAHEY, Boston.

Transurethral Surgery, Its Indications, Limitations and Complications. HERMON C. BUMPUS, JR., Pasadena.

Title to be selected. WILLIAM F. RIENHOFF, JR., Baltimore.

At this year's Congress we will be honored by the presence of a number of distinguished foreign surgeons. Among those who will attend are the following: William F. Shaw, Manchester, England; Archibald H. McIndoe, London, England; J. P. Lockhart-Mummery, London, England; Alexander MacLennan, Glasgow, Scotland; Josef Halban, Vienna, Austria; Alan Newton, Melbourne, Australia; Paul Clairmont, Zurich, Switzerland; Martin Kirschner, Heidelberg, Germany; Wolfgang Rosenthal, Leipzig, Germany; Dr. F. Sauerbruch, Berlin, Germany; and Rodolfo E. Pasman, Buenos Aires, Argentina.

SPECIAL FEATURES OF THE PROGRAM

Special features of the program for this year's Congress include: (1) A conference on fractures under the auspices of the Committee on Fractures; (2) a symposium on cancer arranged by the Committee on the Treatment of Malignant Diseases, (3) a conference on industrial medicine and traumatic surgery under the auspices of the Committee on Industrial Medicine and Traumatic Surgery.

The showing of surgical motion pictures, demonstrating clinical features of interest, has met with popular acceptance in recent years and will be continued at this year's Congress with an enlarged program of films, both sound and silent, to be exhibited daily at headquarters.

HOSPITAL CONFERENCE

The annual hospital conference will open the Congress with a session in the Rose Garden of the Bellevue-Stratford Hotel at 10 o'clock on Monday morning. An interesting program of papers, round table conferences, and practical demonstrations dealing with problems related to hospital efficiency is being prepared for sessions on Monday, Tuesday, Wednesday and Thursday. It is proposed to make this year's program of wide interest and practical character through a careful selection of subjects to be presented and discussed by surgeons and hospital executives, particular emphasis being directed toward professional standards and the vital problems related to hospital economics.

HEADQUARTERS—TECHNICAL EXHIBITION

Clinical Congress headquarters will be established at the Bellevue-Stratford Hotel, which has unusual facilities for accommodating the Congress. The grand ballroom, Garden, Clover and Red Rooms and other large rooms on the first and second floors and the roof have been reserved for scientific sessions and conferences, registration and clinic ticket bureaus, bulletin boards, executive offices, etc. Thus, the activities of the Congress will be centralized under one roof.

The Technical Exhibition will be located in the ballroom and adjacent large rooms on the second floor. The registration and clinic ticket desk, together with the information bureau, will be centrally located as regards the exhibit rooms, in which will be placed the bulletin boards on which the daily clinical program will be posted each afternoon. Leading manufacturers of surgical instruments and supplies, x-ray apparatus, operating room lights, hospital apparatus and supplies of all kinds, ligatures, dressings, pharmaceuticals and publishers of medical books will be represented in this Exhibition.

ADVANCE REGISTRATION

The hospitals and medical schools of Philadelphia afford accommodations for a large number of visiting surgeons, but to insure against overcrowding, attendance at the Congress will be limited to a number that can be comfortably accommodated at the clinics—the limit of attendance being based upon the result of a survey of the amphitheaters, operating rooms, and laboratories of the hospitals and medical schools to determine their capacity for visitors. It is expected, therefore, that those surgeons who wish to attend the Congress will register in advance.

Admittance to all clinics and demonstrations will be controlled by means of special clinic tickets, which plan provides an efficient means for the distribution of the visiting surgeons among the several clinics and insures against overcrowding, as the number of tickets issued for any clinic will be limited to the capacity of the room in which that clinic is given.

A registration fee of $5.00 is required of each surgeon attending the annual Clinical Congress, such fees providing the funds with which to meet the expenses of the meeting. To each surgeon registering in advance a formal receipt for the registration fee is issued, which receipt is to be exchanged for a general admission card upon his registration at headquarters. This card, which is non-transferable, must be presented in order to secure clinic tickets and admission to the evening meetings.